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Opinion

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Nanoparticles as mitochondria-targeted photosensitizer in photodynamic therapy of cancer

Mei-Jie Jou[1,2*] and Tsung-I Peng[2,3]

[1]Department of Physiology and Pharmacology, College of Medicine, Chang Gung University, Tao-Yuan, Taiwan

[2]Department of Neurology, Chang Gung Memorial Hospital, Keelung Branch, Keelung, Taiwan

[3]Department of Medicine, Chang Gung University, Tao-Yuan, Taiwan

Photodynamic effect of mitochondria-targeted photosensitizers

Photodynamic therapy (PDT) is a novel and promising treatment for cancer treatment, which involves the administration of photosensitizers coupled with a specific wavelength of laser irradiation. In the presence of oxygen, the PDT with particular photosensitizer causes significant formation of singlet oxygen as well as other reactive oxygen species (ROS), which produce severe peroxidative reaction as a major contribution to light-induced cell damage and death. To achieve the best efficacy of PDT, an ideal photosensitizer obliges good tissue penetration, low dark toxicity (effect of photosensitizer alone) and high extinction coefficient. In addition, subcellular distribution of photosensitizers appears to be critically involved in the potency of PDT [1]. Recently, the mitochondrion has been considered as a novel pharmacological target for clinical application including cancer therapy due to its crucial role involved in arbitrating cell apoptosis. Mitochondrial dysfunction leads not only to the interruption of ATP supply but also to the activation of mitochondrial dysfunction-mediated apoptotic pathway. Key mitochondrial mechanism involved is the opening of the mitochondrial permeability transition pore (MPTP), which results in mitochondrial membrane potential ($\Delta\psi m$) depolarization, mitochondrial swelling and release of mitochondrial apoptotic lethal proteins to the cytosol. Subsequently, downstream caspases dependent or independent nuclear proteases are activated to cleave nuclear DNA to small fragments. Intriguingly, mitochondria-associated apoptotic mechanisms, particularly the opening of the MPTP and the release of mitochondrial lethal proteins can be initiated and augmented by mitochondrial ROS (mROS) formation as well as mitochondrial free calcium (mCa^{2+}) overload [2-8]. Thus, PDT with an ideal photosensitizer that is able to localize in the mitochondria may significant promote the generation of mROS and then mROS-dependent mCa^{2+} elevation. These two PDT-induced pathological conditions may then interact together to achieve a vicious augmentation of mitochondrial dysfunction and to ensure a potent and successful cell apoptosis for a high efficacy of PDT for tumor eradication.

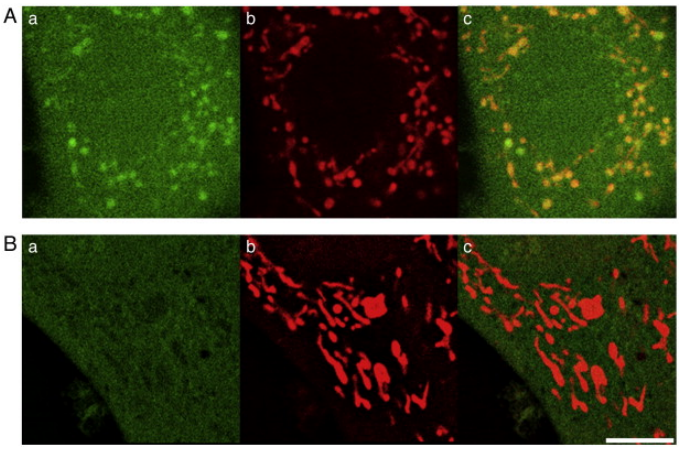

Figure 1. PDE of 488 nm laser coupled C_3-induced mROS "hot spots" and Mito Q-induced "cold spots". A) In the absence of Mito Q. B) In the presence of MitoQ (100 nM). PDE of C_3 (100 μM) was coupled with 60 s of 488 nm laser irradiation. Aa and Ba, DCF images; Ab and Bb, TMRM image; Ac and Bc merged image of DCF and TMRM. Bar, 5 μm.

Mitochondria-targeted nanoparticle photosensitizers: quantum dots (QDs) and carbon sixty (C60)

The high photosensitizing character of nano-semiconductor QDs provides great therapeutic potential in cancer therapy [9,10]. Using laser scanning confocal microscopy we demonstrated QDs localized into the mitochondria. Upon visible light coupled PDE of QDs, mROS-mediated apoptosis was observed. The mitochondrial protector, melatonin, and the mitochondria-targeted antioxidant MitoQ significantly inhibited visible light coupled PDE of QDs-induced apoptosis [11]. Similarly, carbon nanoparticle fullerenes (C_{60}) possess also unique photosensitizing character. Recent chemical modifications on the C60 sphere including tris-malonic acid fullerene (C_3) increases significantly

Correspondence to: Jou MJ, Department of Physiology and Pharmacology, College of Medicine, Chang Gung University, Tao-Yuan, and Department of Neurology, Chang Gung Memorial Hospital, Keelung Branch, Keelung, Taiwan, E-mail: mjjou@mail.cgu.edu.tw

Special Issue: Nanotechnology: Challenges and Perspectives in Medicine

Dr. Federica Valentini
Department of Sciences and Chemical Technologies
Tor Vergata University
Italy

Maurizio Talamo
Professor
Department of Enterprise Engineering
Italy

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its solubility in water and hence its application in disease-based nano-biomedical science [12,13]. PDE of C_3 (100 nM) coupled with 488 nm laser induces significant mROS formation and Δψm depolarization which causes marked fission and swelling of mitochondria (Figure 1). Mitochondrial hot spots due to significant mROS formation caused significant loss of TMRM indicating depolarized $\Delta_{\psi m}$ [14]. PDE of visible light coupled mitochondria-targeted nano photosensitizers via enhancing mROS-mediated mitochondrial stress leading to enhanced apoptosis or necrosis. Thus, these nanoparticle-coupled photodynamic therapy may serve as a potential maneuver for clinical treatment of tumors and cancer in the CNS including glioma and astrocytoma.

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