ENHANCED NIR RADIATION-TRIGGERED HYPERTHERMIA BY MITOCHONDRIAL TARGETING

J. Am. Chem. Soc., 2015, 137, 3017-3023

Tanja Krainz
Current Literature
December 19, 2015
What is ‘Hyperthermia’?

*Hyperthermia* (also called *thermotherapy*) is a type of *cancer treatment* in which body tissue is exposed to high temperatures up to 45 °C (113°F)

- **Local Hyperthermia** (Thermal ablation): Very high temperatures can be used to destroy a small area of cells, such as a tumor (depending on location of tumor heat may be applied via needles or probes)
- **Regional Hyperthermia**: The temperature of a part of the body (limb or whole organ) can be raised a few degrees higher than normal. It helps other cancer treatments such as radiation, immunotherapy, or chemotherapy work better.
- **Whole body Hyperthermia**: Typically used to treat metastatic cancer. Temperature is being raised to 39-42 °C (102 -109F); sometimes even higher.
Heat Sources and Common Challenges

Common Sources:
- Focused Ultrasound
- Infrared sauna
- Microwave heating
- Induction heating
- Magnetic hyperthermia

Common Challenges
- Controlling temperature
- Toxicity resulting from nanoparticles

In order to achieve higher radiation to heat conversion in hyperthermia with NIR sensitive magnetic particles, the delivery of large amounts of MPs has been pursued; however, this method can increase the damage to normal cells too.

Heat delivery to mitochondria may enhance hyperthermic cytotoxicity
This study: Hyperthermia in Mitochondria

Mitochondria are highly sensitive to heat shock, frequently causing cell death by overproduction of ROS.

Magnetic Nanoparticles

Iron Oxide Particles: nontoxic, biocompatible, compatible with magnetic resonance imaging technology.

Goal: Enhance cytotoxicity for a given amount of heat by selectively delivering MPs to mitochondria with minimal side effects.
Synthesis of Mito-CIO and CIO

1. Isobutylchloroformate
N-Methylmorpholine
DMF
2. PPh₃(CH₂)₂NH₂Cl-
N-Methylmorpholine
52% (over 2 steps)
Characterization of Mito-CIO

a. TEM Image of Mito-CIO
b. UV-Vis absorption of Mito-CIO and 2
c. TEM mapping image; (i) bright field image; (ii) iron; (iii) oxygen; (iv) nitrogen; (v) phosphorus components
Photothermal Conversion Efficiency

- Irradiation with 740nm NIR laser at 2W/cm²
- Gradual increase of laser power over time

These results demonstrate that the heat is generated by NIR irradiation of the iron-oxide based Mito-CIO with an excellent Photothermal Conversion Efficiency.
Photothermal Conversion Efficiency in HeLa Cells

- Temperature of HeLa cells loaded with Mito-CIO was monitored under constant NIR irradiation using an infrared thermal camera.

10W/cm² irradiation with a 740nm NIR laser rapidly elevated temperature of HeLa cells by $2.14 \pm 0.25$ °C within 5 min.

These results demonstrate that Mito-CIO is capable of elevating the cell temperature upon NIR irradiation.
Cytotoxicity of Mito-CIO-Loaded HeLa Cells

HeLa Cells were prestained with propidium iodide and calcein AM

Fluorescence microscopic results reveal more rapid and extensive cell death for Mito-CIO than CIO.

Cytotoxicity induced by irradiated Mito-CIO reached $89.90 \pm 7.72\%$ within 20 min.
*In Vivo Xenograft Tumor Imaging and Therapy using MPs*

Ex vivo fluorescence in various tissues: (i) liver; (ii) kidney; (iii) tumor; (iv) heart; (v) lung; (vi) spleen tissue
After six doses with NIR irradiation on one side of the grafted tumor region, the irradiated tumor volume in the Mito-CIO group was significantly reduced compared to the non-irradiated tumor volume.
Conclusion

- Prepared a new mitochondria-targeting iron-oxide NP with an efficient photothermal conversion efficiency
- Induces enhanced cytotoxicity in HeLa cells
- In vivo therapy clearly displays tumor suppression

These findings strongly support the hypothesis that mitochondria are more susceptible to hyperthermia than ER.