Research Highlight #145

Novel Applications of Mitochondria-Targeted Nitroxides in Cancer Treatment

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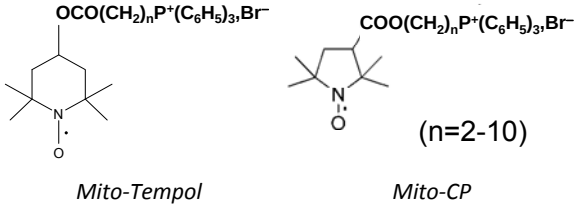
Mitochondria-targeted nitroxides (MTNs) (Mito-Tempol, Mito-CP) are a group of compounds generated by conjugating a positively-charged triphenylphosphonium moiety to a simple nitroxide (Tempol and carboxy proxyl) *via* an alkyl chain. Depending on the carbon-carbon chain length, a variety of short and long-chain MTNs (Mito-CP_{11}, Mito-CP_4) can be synthesized. MTNs (with a positive charge) are taken up into mitochondria (with a negative membrane potential) to a varying degree depending on their chain lengths. MTNs protect against the oxidative damage induced by radiation and antitumor agents in normal cells. However, MTNs are "mitochondriotoxic" in most tumor cells. Emerging research in cancer chemotherapy is focused on exploiting the biochemical differences between cancer cell and normal cell metabolism. In cancer cells, there is a shift in energy metabolism from oxidative phosphorylation to glycolysis to generate ATP (the Warburg effect). Agents [*e.g.*, 2-deoxy-D-glucose (2-DG)] that specifically inhibit glycolytic metabolism have been used as effective anticancer agents. We observed that MTNs synergistically enhanced 2-DG-mediated breast and pancreatic cancer cell death. MTN (Mito-CP_{11}) treatment dramatically affected the cellular bioenergetic function and ATP levels in breast cancer cells (MCF-7) but not in control noncancerous cells (MCF-10A). Similarly, MTN and 2-DG synergistically enhanced pancreatic cancer cell death. Targeting mitochondrial bioenergetic metabolism with cationic MTN and glycolytic inhibitors is a potentially promising chemotherapeutic therapy. The dual mechanism (cytoprotection in normal cells and cytotoxicity in cancerous cells) of mitochondria-targeted nitroxides may also be responsible for overcoming drug resistance.



Mito-Tempol *Mito-CP*

Cheng G, Lopez M, Zielonka J, Hauser AD, Joseph J, McAllister D, Rowe JJ, Sugg SL, Williams CL, Kalyanaraman B. Mitochondria-targeted nitroxides exacerbate Fluvastatin-mediated cytostatic and cytotoxic effects in breast cancer cells. Cancer Biol. Ther. (2011) 12:707-717; PMC3218525.

Mukhopadhyay P, Horvath B, Zsengeller Z, Zielonka J, Tanchian G, Holovac E, Kechrid M, Patel V, Stillman IE, Parikh SM, Joseph J, Kalyanaraman B, Pacher P. Mitochondrial-targeted antioxidants represent a promising approach for prevention of cisplatin-induced nephropathy. Free Radic. Biol. Med. (2012) 52:497-506; PMC3253235.