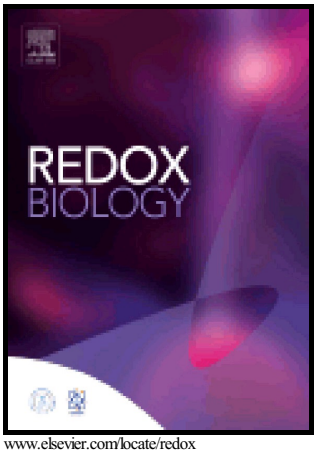

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A review of the basics of mitochondrial bioenergetics, metabolism, and related signaling pathways in cancer cells: Therapeutic targeting of tumor mitochondria with lipophilic cationic compounds

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Abstract

The present review is a sequel to the previous review on cancer metabolism published in this journal. This review focuses on the selective antiproliferative and cytotoxic effects of mitochondria-targeted therapeutics (MTTs) in cancer cells. Emerging research reveals a key role of mitochondrial respiration on tumor proliferation. Previously, a mitochondria-targeted nitroxide was shown to selectively inhibit colon cancer cell proliferation at submicromolar levels. This review is centered on the therapeutic use of MTTs and their bioenergetic profiling in cancer cells. Triphenylphosphonium cation conjugated to a parent molecule (*e.g.*, vitamin-E or chromanol, ubiquinone, and metformin) *via* a linker alkyl chain is considered an MTT. MTTs selectively and potently inhibit proliferation of cancer cells and, in some cases, induce cytotoxicity. MTTs inhibit mitochondrial complex I activity and induce mitochondrial stress in cancer cells through generation of reactive oxygen species. MTTs in combination with glycolytic inhibitors synergistically inhibit tumor cell proliferation. This review discusses how signaling molecules traditionally linked to tumor cell proliferation affect tumor metabolism and bioenergetics (glycolysis, TCA cycle, and glutaminolysis).

Keywords: triphenylphosphonium cation; pancreatic ductal adenocarcinoma; extracellular acidification rate; oxygen consumption rate; coenzyme Q_{10}