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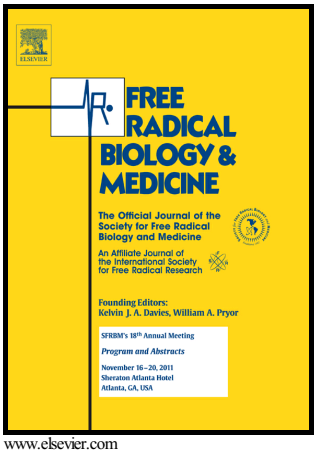

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Low energy costs of F1Fo ATP synthase reversal in colon carcinoma cells deficient in mitochondrial complex IV

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Abstract

Mitochondrial polarisation is paramount for a variety of cellular functions. Under ischemia, mitochondrial membrane potential (ΔΨm) and proton gradient (ΔpH) are maintained via a reversal of mitochondrial F1Fo ATP synthase (mATPase), which can rapidly deplete ATP and drive cells into energy crisis. We found that under normal conditions in cells with disassembled cytochrome c oxidase complex (COX-deficient HCT116), mATPase maintains ΔΨm at levels only 15-20% lower than in WT cells, and for this utilises relatively little ATP. For a small energy expenditure, mATPase enables mitochondrial ΔpH, protein import, Ca^{2+} turnover, and supports free radical detoxication machinery enlarged to protect the cells from oxidative damage. Whereas in COX-deficient cells the main source of ATP is glycolysis, the ΔΨm is still maintained upon inhibition of the adenine nucleotide translocators with bongkrekic acid and carboxyatractyloside, indicating that the role of ANTs is redundant, and matrix substrate level phosphorylation alone or in cooperation with ATP-Mg/P_i carriers can continuously support the mATPase activity. Intriguingly, we found that mitochondrial complex III is active, and it contributes not only to free radical production, but also to ΔΨm maintenance and energy budget of COX-deficient cells. Overall, this study demonstrates that F1Fo ATP synthase can support general mitochondrial and cellular functions, working in extremely efficient 'energy saving' reverse mode and flexibly recruiting free radical detoxication and ATP producing / transporting pathways.

Abbreviations

ANT: adenine nucleotide translocator; ATP5A1: ATP synthase; H^+ transporting, mitochondrial F1 complex, alpha subunit 1; BKA: bongkrekic acid; COX: cytochrome c oxidase (mitochondrial complex IV); ECA: extracellular acidification; ETC: electron transport chain; G6PD: glucose-6-phosphate dehydrogenase; GSH: glutathione; NNT: nicotinamide nucleotide transhydrogenase; OxPhos: oxidative phosphorylation; PMF: proton motive force; PMPI: plasma membrane potential indicator; SCO2: synthesis of cytochrome c oxidase 2; SUCLA2: succinate-CoA ligase 2, ADP-forming, beta subunit; TIM: transporter inner membrane; TMRM: tetramethyl rhodamine methyl ester;