

A Mitochondria-K⁺ Channel Axis Is Suppressed in Cancer and Its Normalization Promotes Apoptosis and Inhibits Cancer Growth

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SUMMARY

The unique metabolic profile of cancer (aerobic glycolysis) might confer apoptosis resistance and be therapeutically targeted. Compared to normal cells, several human cancers have high mitochondrial membrane potential ($\Delta\Phi_m$) and low expression of the K⁺ channel Kv1.5, both contributing to apoptosis resistance. Dichloroacetate (DCA) inhibits mitochondrial pyruvate dehydrogenase kinase (PDK), shifts metabolism from glycolysis to glucose oxidation, decreases $\Delta\Phi_m$, increases mitochondrial H₂O₂, and activates Kv channels in all cancer, but not normal, cells; DCA upregulates Kv1.5 by an NFAT1-dependent mechanism. DCA induces apoptosis, decreases proliferation, and inhibits tumor growth, without apparent toxicity. Molecular inhibition of PDK2 by siRNA mimics DCA. The mitochondria-NFAT-Kv axis and PDK are important therapeutic targets in cancer; the orally available DCA is a promising selective anticancer agent.