

Cellular succinate transport and mitochondrial respiratory function in prostate cancer

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Succinate dehydrogenase (SDH, mitochondrial Complex II) links the oxidation of succinate and FAD to fumarate and FADH₂ in the tricarboxylic acid (TCA) cycle to electron transfer (ET) from FADH₂ to ubiquinone in the ET system. Changes in ET capacity through the succinate pathway affect TCA cycle function and cell respiration [1]. In addition, succinate transmits oncogenic signals from mitochondria to the cytosol by stabilization of hypoxia inducible factor 1 α . This, in turn, stimulates the expression of genes involved in angiogenesis and anaerobic metabolism [2], finally enabling tumour progression and metastasis. Succinate uptake is enhanced in various cancer cells [3] and its mitochondrial utilisation is increased in permeabilized prostate cancer cells [4].

To decipher the pathophysiological role of succinate in prostate cancer, we tested the plasma membrane permeability for succinate and utilization of external succinate by mitochondria in terms of succinate pathway capacity and kinetic properties in prostate cancer (multiple metastatic origins) and control cell lines. Respiration in RWPE-1 (prostate; noncancerous), LNCaP (prostate; lymph node metastasis) and DU145 (prostate; brain metastasis) cells was measured using High-Resolution Fluorescence Respirometry (O2k, Oroboros Instruments) and substrate-uncoupler-inhibitor titration (SUIT) protocols developed specifically for the study. To assess succinate utilization in intact cells independent of a plasma membrane succinate transporter, we applied novel plasma membrane-permeable succinate prodrugs (pS) [5].

In LNCaP cells, transport of external succinate is enhanced through the plasma membrane as compared to the other cell lines, while pS exerted similar effects in all cell lines, suggesting an important regulatory role of the transport mechanism. Furthermore, in LNCaP cells, mitochondria utilize succinate with higher affinity than control cells. Importantly, kinetic measurements demonstrated the most pronounced difference in the affinities in the physiological intracellular succinate concentration range (< 100 μ M), underlining its pathophysiological role.

Our results indicate a “succinate-phenotype” in LNCaP, with enhanced transport and utilization. As such, succinate is a potential mitochondrial metabolic biomarker in prostate cancer cells. We propose a model in which succinate does not only play a role in the signalling but has a central role in the maintenance of mitochondrial respiration as a fuel substrate.

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