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## **Mitochondrial uncoupling and the Warburg effect: Molecular basis for the reprogramming of cancer cell metabolism**

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### **Abstract**

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The precise mitochondrial alterations that underlie the increased dependence of cancer cells on aerobic glycolysis for energy generation have remained a mystery. Recent evidence suggests that mitochondrial uncoupling – the abrogation of ATP synthesis in response to mitochondrial membrane potential – promotes the Warburg effect in leukemia cells, and may contribute to chemoresistance. Intriguingly, leukemia cells cultured on bone marrow-derived stromal feeder layers are more resistant to chemotherapy, increase the expression of uncoupling protein 2, and decrease the entry of pyruvate into the Krebs cycle – without compromising the consumption of oxygen, suggesting a shift to the oxidation of non-glucose carbon sources to maintain mitochondrial integrity and function. Since fatty acid oxidation has been linked to chemoresistance and mitochondrial uncoupling, it is tempting to speculate that Warburg's observations may indeed be the result of the preferential oxidation of fatty acids by cancer cell mitochondria. Therefore, targeting fatty acid oxidation or anaplerotic pathways that support fatty acid oxidation may provide additional therapeutic tools for the treatment of hematopoietic malignancies.

**Keywords:** Warburg effect, uncoupling proteins, mitochondria, leukemia, Krebs cycle

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### **The Warburg effect and mitochondrial uncoupling**

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More than half a century ago Otto Warburg proposed that cancer cells originated from non-neoplastic cells that acquired a permanent respiratory defect that bypassed the Pasteur effect, i.e. the inhibition of fermentation by oxygen (1). This hypothesis was based on results of extensive characterization of the fermentation and oxygen consumption capacity of normal and malignant tissues – including mouse ascites and Earle’s cells of different malignancies but same genetic origin – that conclusively demonstrated a higher ratio of fermentation to respiration in the neoplastic cells. Moreover, the data indicated that the more malignant Earle’s cancer cells displayed a higher ratio of fermentation to respiration than their less malignant counterparts, suggesting to Warburg and his colleagues that a gradual and cumulative decrease in mitochondrial activity was associated with malignant transformation. Interestingly, the precise nature of these gradual and cumulative changes has eluded investigators for nearly 80 years, albeit Warburg’s observations of an increased rate of aerobic glycolysis in cancer cells have been reproduced countless times – not to mention the wealth of positron emission tomography images that support an increased uptake of radiolabeled glucose in tumor tissues.

It is noteworthy that while Warburg’s hypothesis remains a topic of discussion amongst cancer biologists, Otto Warburg himself had alluded to an alternative hypothesis put forth by Feodor Lynen – one which did not necessitate permanent or transmissible alterations to the oxidative capacity of mitochondria – that suggested the possibility that the increased dependence of cancer cells on glycolysis stemmed not from their inability to reduce oxygen, but rather from their inability to synthesize ATP in response to the mitochondrial proton gradient ( $\Delta\Psi$ ) (1). Lynen’s hypothesis was partly based on his work (2) and the previous work of Ronzoni and Ehrenfest utilizing the prototypical protonophore 2,4-dinitrophenol (DNP) which causes a “short circuit” in the electrochemical gradient that abolishes the mitochondrial synthesis of ATP, and decreases the entry of pyruvate into the Krebs cycle (3). Subsequent work demonstrated that mitochondrial uncoupling (i.e., the abrogation of ATP synthesis in response to  $\Delta\Psi$ ) results in a metabolic shift to the utilization of non-glucose carbon sources to maintain mitochondrial function (4,5). Given the elusiveness of permanent transmissible alterations to the oxidative capacity of cancer cells that could broadly support Warburg’s hypothesis, could Lynen’s hypothesis better explain the dependence of cancer cells on glycolysis for ATP generation?

Over the past several decades it has become increasingly clear that mitochondrial uncoupling occurs under physiological conditions, such as during cold acclimation in mammals, and is mediated, at least in part, by uncoupling proteins (UCPs) (6,7). UCP1 was the first uncoupling protein identified, and was shown to play a role in

energy dissipation as heat in mammalian brown fat (6). During cold acclimation, UCP1 accumulates in the inner mitochondrial membrane and short circuits  $\Delta\Psi_M$  (created by the mitochondrial respiratory chain) by sustaining an inducible proton conductance (7). Other UCPs have been identified in humans (UCP2-4), albeit their functions may be unrelated to the maintenance of core body temperature, and instead involved in the reprogramming of metabolic pathways. For instance, recent work demonstrates that UCP2 is necessary for efficient oxidation of glutamine (8), and may promote the metabolic shift from glucose oxidation to fatty acid oxidation (4). Likewise, UCP3 has also been shown to promote fatty acid oxidation in muscle tissue via, in part, an increased flux of fatty acid anions (9), however, like for UCP2, the nature of its proton conductance remains controversial (reviewed in (10)). More interesting perhaps, are recent observations that UCP2 is overexpressed in various chemoresistant cancer cell lines and primary human colon cancer, and that overexpression of this uncoupling protein leads to an increased apoptotic threshold (11) – suggesting that in addition to metabolic reprogramming, uncoupling proteins may *ipso facto* provide a prosurvival advantage to malignant cells.

It is important to point out that physiological fatty acid oxidation has been shown to be associated with an uncoupling and/or thermogenic phenotype in various cell types (reviewed in (12)). In addition, it is also significant that glycolysis derived pyruvate – as well as  $\alpha$ -ketoglutarate derived from glutaminolysis – may be necessary to provide anaplerotic substrates (i.e. those that replenish intermediates in metabolic cycles) for efficient Krebs cycle utilization of fatty acid-derived acetyl CoA (13) suggesting the possibility that in certain cell types high rates of aerobic glycolysis may be necessary for efficient mitochondrial oxidation of fatty acids (“fats burn in the fire of carbohydrates”). The above support the concept – and indirectly, Lynen’s hypothesis – that the Warburg effect may in fact be the result of fatty acid and/or glutamine oxidation in favor of pyruvate utilization.