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Review

Cancer cell metabolism and mitochondria: Nutrient plasticity for TCA cycle fueling

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ABSTRACT

Warburg's hypothesis that cancer cells take up a lot of glucose in the presence of ambient oxygen but convert pyruvate into lactate due to impaired mitochondrial function led to the misconception that cancer cells rely on glycolysis as their major source of energy. Most recent ^{13}C-based metabolomic studies, including in cancer patients, indicate that cancer cells may also fully oxidize glucose. In addition to glucose-derived pyruvate, lactate, fatty acids and amino acids supply substrates to the TCA cycle to sustain mitochondrial metabolism. Here, we discuss how the metabolic flexibility afforded by these multiple mitochondrial inputs allows cancer cells to adapt according to the availability of the different fuels and the microenvironmental conditions such as hypoxia and acidosis. In particular, we focused on the role of the TCA cycle in interconnecting numerous metabolic routes in order to highlight metabolic vulnerabilities that represent attractive targets for a new generation of anticancer drugs.

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1. Introduction

The Warburg paradigm as the prototypical model of cancer metabolism (*i.e.* preferred aerobic glycolysis and dysfunctional mitochondria in tumor cells) has been the subject of profound reappraisal in the last decade. Cancer cells can indeed use a variety of fuels distinct from glucose to support proliferation and/or survival [1]. Also, accumulating evidence now suggests that mitochondrial metabolism is required for tumorigenesis [2]. Recent studies actually showed that in various tumor types, treatment-resistant cancer cells [3], metastatic/circulating cancer cells [2,4], cancer stem cells (CSC) and tumor-initiating cells (TIC) [5,6] rely on mitochondrial respiration. Moreover, key metabolic enzymes and pathways associated with the mitochondrial metabolism were documented to support tumor progression driven by major oncogenes [7–9].

Heterogeneity in the metabolic preferences was also reported within a given tumor. The mitochondrial oxidation of multiple nutrients may actually co-exist with an enhanced glycolytic pathway (*i.e.* with lactate as end-product) [10]. A role of the tumor microenvironment in the

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oxidative fate of various nutrients was further elicited using *in vivo* isotope tracking [11] and this metabolic heterogeneity in primary tumor was shown to be associated with distinct sites of metastatic spreading [8]. All the above studies have to some extent paved the way of how, by targeting metabolic pathways to which cancer cells may be addicted, eradication of the most life-threatening tumor cells may be envisioned.

1.1. Metabolomic studies in cancer patients shake the Warburg dogma

Stable isotope tracers (*e.g.* ^{13}C) can be used to investigate cellular metabolism, in particular to track the fate of biosynthetic fuels through the analysis of isotope enrichment downstream of labeled nutrients [12]. This approach has been increasingly used in various mouse models in the last decade [13,14] and more recently in cancer patients. The first human cancers investigated with these tracers are glioma, brain metastases and non-small cell lung cancer (NSCLC) [15,16]; classically, tracers are bolus-administered or infused during surgical resection, and tumor samples are subsequently subjected to ^{13}C NMR spectroscopy. The first observations resulting from these metabolomic studies in cancer patients were that (i) glucose is metabolized not only through glycolysis (*i.e.* up to lactate production) but also through the mitochondrial TCA cycle and (ii) a significant fraction of the acetyl-CoA used in the TCA cycle is not derived from blood-borne glucose [15,16].

More recently, Hensley and colleagues added a layer of sophistication to these studies [10]. They actually assessed tumors in untreated NSCLC patients prior to surgery, using [^{18}F]fluoro-2-deoxy-glucose (FDG) PET imaging and multiparametric MRI including dynamic contrast-enhanced MRI (DCE-MRI) to assess perfusion. Here again, besides the expected enhanced glycolytic flux, they found evidence for oxidation of a large variety of other nutrients. These data further suggest that metabolic heterogeneity between and within tumors can be predicted by assessing tissue perfusion preoperatively. These authors actually proposed that substrates other than glucose would preferentially contribute to the TCA cycle in well-perfused tumor areas whereas glucose oxidation would occur in less perfused tumor regions (where it remains available by virtue of its high concentration and capacity to diffuse). Although there are obvious limitations in the use of DCE-MRI to compare the perfusion in tumors from different patients and in different regions from a same tumor, these results suggest that the local microenvironment may override apparent oncogene-driven metabolic preferences identified in *in vitro* studies. Altogether, the above studies shake the dogma according to which a FDG-PET-positive signal is necessarily correlated with the Warburg effect or so-called aerobic glycolysis. Similar conclusions were recently reached by comparing the fate of isotope-labeled glucose or glutamine in cultured cells *vs.* mouse lung tumors [11]. Deletion of enzymes involved in glucose oxidation (*i.e.* pyruvate dehydrogenase (PDH) and pyruvate carboxylase (PC)) actually prevented tumor growth while having no effect on *in vitro* cell growth (see below). Also, while glutaminase (GLS) deletion had no effect on tumor burden *in vivo*, tumor-derived cell lines were highly glutaminolytic and sensitive to GLS inhibitors [11].

The application of metabolomics to cancer patients is still in its infancy and some issues still need to be addressed, such as the presence of stromal cells in the collected tumor fragments and their exact contribution to the measured metabolite enrichment. Other issues would deserve more attention. For instance, the ligation of feeding arteries prior to resection could confuse the interpretation of the preferential use of ^{13}C-labeled nutrients in tumors of cancer patients. Also, the organ of cancer origin could account for major differences because metabolism is optimized in each tissue to match physiological functions and energy/fuel requirements. Pre-existing metabolic peculiarities of a given tissue will thus combine with oncogenic rewiring of the metabolism to support bioenergetic and biosynthetic needs of a given cancer. This complicates the task to associate metabolic preferences with a cancer type or an oncogene. For instance, MYC-driven liver and triple-negative breast cancers are more glutamine-dependent than MET-driven liver and MYC-driven lung tumors [14,17,18]. Besides these caveats, *in vivo* metabolic and metabolomic studies point towards mitochondria as an unavoidable target in the design of further therapeutic strategies aiming to interfere with the metabolism of glucose, lactate, fatty acids and glutamine (Fig. 1).

1.2. Mitochondria represent a necessary hub in the cancer cell bioenergetics network

The identification of mutations in enzymes of the TCA cycle including succinate dehydrogenase (SDH), fumarate hydratase (FH) and isocitrate dehydrogenase (IDH) [19,20], has emphasized how alterations in the mitochondrial component of cancer cell metabolism may dramatically alter cell bioenergetics and offer new therapeutic avenues. In cancer cells that do not exhibit mutations in the TCA cycle enzymes, mitochondria operate as a central hub of both catabolic and anabolic metabolism in cancer cells. Here, we outline the critical biosynthetic functions served by mitochondria within tumors with a focus on the peculiarities that may render some metabolic pathways druggable, *i.e.* differentially regulated (*vs.* healthy tissues). The goal of this review is however not to discuss about mitochondrial electron transfer chain (ETC) as a potential therapeutic target and about drugs that in part *via* inhibition of ETC complexes (*e.g.* metformin or phenformin) may perturb mitochondrial oxidative phosphorylation (OXPHOS). Instead, we chose to put into perspective recent insights in the understanding of the TCA cycle fueled by pyruvate, lactate, glutamine and fatty acids (Fig. 1), and the effects (and limitations) of drugs targeting these pathways.

2. Pyruvate reductive and oxidative metabolism

The last step of glycolysis is the production of pyruvate by pyruvate kinase (PK). Pyruvate can either be reduced in the cytosol or transported into mitochondria to be oxidized. Pyruvate reduction into lactate through LDHA generates NAD^+ that is required to restore the NAD^+ pool to maintain a high glycolytic rate (Fig. 2). Of note, LDH

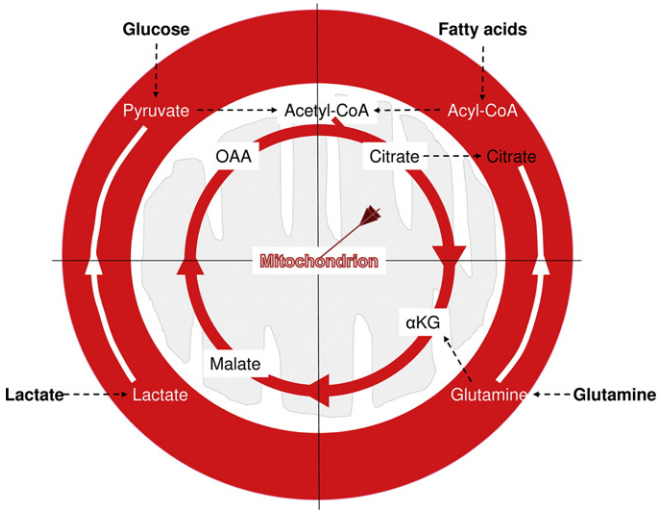

Fig. 1. Mitochondrial metabolism as a therapeutic target. Mitochondria represent a hub for a variety of biosynthetic and bioenergetic pathways fueled by glucose, pyruvate, fatty acids and glutamine. Although part of the glucose is converted into lactate to support a high glycolytic rate, there is now enough evidence to claim that the activity of the TCA cycle, coupled or not to oxidative phosphorylation, represents an obligatory support to tumor cell growth. Addictions to TCA-related metabolic pathways driven by specific oncogenes or the selective pressure of the microenvironment (*e.g.* acidosis, moderate hypoxia, nutrient availability) therefore represent a source of potential targets for a new category of anticancer drugs.