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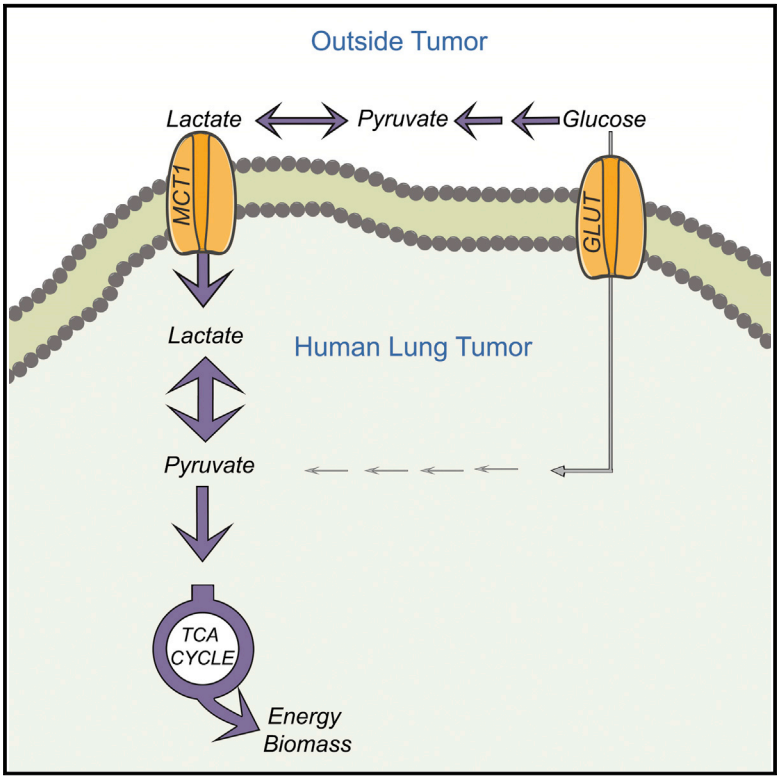
Lactate Metabolism in Human Lung Tumors

Graphical Abstract



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In Brief

Human non-small cell lung cancer preferentially utilizes lactate over glucose to fuel TCA cycle and sustain tumor metabolism *in vivo*.

Highlights

- Lactate is metabolized by human lung tumors *in vivo*
- Lactate use correlates with high FDG-PET signal and occurs in diverse oncogenotypes
- MCT1 enables lactate consumption by some lung cancer xenografts
- Lactate's contribution to the TCA cycle *in vivo* exceeds that of glucose

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Lactate Metabolism in Human Lung Tumors

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SUMMARY

Cancer cells consume glucose and secrete lactate in culture. It is unknown whether lactate contributes to energy metabolism in living tumors. We previously reported that human non-small-cell lung cancers (NSCLCs) oxidize glucose in the tricarboxylic acid (TCA) cycle. Here, we show that lactate is also a TCA cycle carbon source for NSCLC. In human NSCLC, evidence of lactate utilization was most apparent in tumors with high ^{18}fluorodeoxyglucose uptake and aggressive oncological behavior. Infusing human NSCLC patients with ^{13}C-lactate revealed extensive labeling of TCA cycle metabolites. In mice, deleting monocarboxylate transporter-1 (MCT1) from tumor cells eliminated lactate-dependent metabolite labeling, confirming tumor-cell-autonomous lactate uptake. Strikingly, directly comparing lactate and glucose metabolism *in vivo* indicated that lactate's contribution to the TCA cycle predominates. The data indicate that tumors, including bona fide human NSCLC, can use lactate as a fuel *in vivo*.

INTRODUCTION

Constitutive glucose uptake is a hallmark of cancer cells and provides energy and biosynthetic material for cancer cell proliferation (Hanahan and Weinberg, 2011). Accordingly, enhanced expression of glucose transporters and glycolytic enzymes is a common consequence of oncogenic signaling and transcriptional networks (Vander Heiden and DeBerardinis, 2017). Glucose uptake is also important for metabolic imaging and staging in cancer. ^{18}fluoro-2-deoxyglucose positron emission tomography (FDG-PET) utilizes the propensity of many solid tumors to take up and retain glucose, providing imaging contrast with adjacent tissue (Fletcher et al., 2008). The metabolic fates of glucose in FDG-PET-positive tumors and the extent to which other fuels complement glucose utilization in these tumors are areas of active study (Davidson et al., 2016; Fan et al., 2009; Hensley et al., 2016; Mashimo et al., 2014).

In cultured cancer cells, most glucose carbon is converted to pyruvate via glycolysis, reduced to lactate via lactate dehydrogenase (LDH), and secreted (DeBerardinis et al., 2008). Disposal of this large carbon pool as lactate serves at least two functions. The NADH-dependent reduction of pyruvate to lactate by LDH recycles the NAD+ reduced to NADH during glycolysis, allowing glycolysis to persist. Excreting lactate through monocarboxylate transporters (MCT; e.g., MCT1, MCT4) eliminates protons arising from the glyceraldehyde 3-phosphate dehydrogenase reaction in glycolysis, thereby maintaining pH homeostasis inside the cell and acidifying the extracellular space. Evidence indicates that lactate in the microenvironment modulates immune cell function and promotes invasion and metastasis, implicating tumor glycolysis and lactate secretion in processes that impact cancer-related mortality (Brand et al., 2016; Rizwan et al., 2013; Xie et al., 2014).

However, other studies have proposed that tumors use lactate as a fuel, expanding its metabolic functions in cancer. Lactate circulates at levels of 1–2 mM and acts as an interorgan carbon shuttle in mammals (Cori and Cori, 1929). Some cancer cells use lactate as a respiratory substrate and a lipogenic precursor in culture (Chen et al., 2016). Blocking lactate uptake with an MCT1 inhibitor reduces respiration and promotes glycolysis in some cancer cell lines and suppresses xenograft growth in mice (Pavlides et al., 2009; Sonveaux et al., 2008). In mouse models of breast cancer, the growth-promoting effect of stromal