Fatty acid labeling from glutamine in hypoxia can be explained by isotope exchange without net reductive IDH flux

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Capsule:

Background: Cancer cells in hypoxia were claimed to rely on reductive isocitrate dehydrogenase (IDH) for lipogenesis based on increased isotopic labeling of fatty acids from glutamine.

Results: Oxidative IDH flux persists in hypoxia while acetyl-CoA demand drops.

Conclusion: Reductive IDH flux may not be a net contributor to acetyl-CoA production.

Significance: Isotopic label incorporation is indicative of flux though not necessarily of net flux.

Abstract

Acetyl-CoA is an important anabolic precursor for lipid biosynthesis. In the conventional view of mammalian metabolism, acetyl-CoA is primarily derived by the oxidation of glucose-derived pyruvate in mitochondria. Recent studies have employed isotope tracers to show that in cancer cells grown in hypoxia or with defective mitochondria, a major fraction of acetyl-CoA is produced via another route, reductive carboxylation of glutamine-derived α-ketoglutarate (catalyzed by reverse flux through isocitrate dehydrogenase, IDH). Here, we employ a quantitative flux model to show that in hypoxia and in cells with defective mitochondria, oxidative IDH flux persists and may exceed the reductive flux. Therefore, IDH flux may not be a net contributor to acetyl-CoA production, though we cannot rule out net reductive IDH flux in some compartments. Instead of producing large amounts of net acetyl-CoA reductively, the cells adapt by reducing their demand for acetyl-CoA by importing rather than synthesizing fatty acids. Thus, fatty acid labeling from glutamine in hypoxia can be explained by spreading of label without net reductive IDH flux.

Introduction

Oxygen limitation leads to genetic and biochemical reprogramming of central metabolism, which increases reliance on glycolysis for energy production (1,2). The transcription factor hypoxia inducible factor HIF1 plays a central role in cellular adaptation to hypoxia, upregulating glucose intake, glycolytic enzymes, and lactate secretion. HIF further suppresses glycolytic flux entering TCA cycle through pyruvate dehydrogenase (PDH) by inducing transcription of pyruvate dehydrogenase kinase 1 (PDK1) which is an inhibitor of PDH(3). In addition to inhibiting glycolytic flux into TCA cycle, HIF activates c-MYC(4), which induces glutamine uptake and catabolism, generating TCA cycle intermediates(5).
Even in the presence of adequate oxygen, tumor cells manifest upregulated glycolysis relative to oxidative phosphorylation (Warburg effect) (6). In most cases this is due to increased glycolysis that is induced by onco gene signaling rather than impairment of mitochondrial function (7). In some tumors, however, mitochondrial function is impaired by mutated mitochondrial proteins. For example, somatic mutations in the TCA cycle genes fumarate hydratase (FH) and succinate dehydrogenase (SDH) are tumorigenic (8). In both cases, the mutations lead to the activation of HIF, which causes a pseudohypoxic state, resulting in similar phenotypes to those of hypoxic cells even in the presence of oxygen.

An important intermediate of oxidative mitochondrial metabolism is acetyl-CoA. Cytosolic acetyl-CoA is the main precursor for de novo fatty acid biosynthesis. The canonical pathway for production of cytosolic acetyl-CoA begins with the oxidation of glucose-derived pyruvate in mitochondria (Figure 1). The resulting mitochondrial acetyl-CoA is consumed by citrate synthase to convert oxaloacetate into citrate. Citrate may then either be oxidized in TCA cycle or shunted to cytoplasm, where its cleavage by ATP citrate lyase produces cytosolic acetyl-CoA (9).

Recent studies have employed isotope tracing to study how acetyl-CoA is produced in mammalian cell by feeding with [13C]-labeled glutamine, glutamate or succinate and measuring the resulting labeling of citrate and fatty acids (10-16). Experiments in liver and cardiac cells established that a fraction of citrate and fatty acid 2-carbon units originates from α-ketoglutarate through reductive carboxylation of isocitrate dehydrogenase (IDH) (14-16). More recently, reductive IDH was claimed to be particularly important in hypoxia and pseudohypoxia, where a major fraction fatty acid carbon units originates from glutamine (10-13).

While these isotope tracer experiments unambiguously demonstrate reverse IDH flux, they do not address the question of whether there is actually net flux in the reductive direction. In general, isotope labeling patterns reflect gross (i.e., total) flux in a given direction, which may be offset by yet greater flux in the opposite direction and not necessarily net conversion. This key principle was elucidated more than half a century ago to refute claims that liver synthesize glucose from fatty acids based on the experimental observation that feeding cells with labeled fatty acids result in glucose labeling (17,18). More recently, Landau and Wahren have emphasized the difference between label incorporation and net flux (19) in the context of identification of pseudoketogenesis which can be misinterpreted to grossly overestimate ketogenesis (20-22).

In this work, we employ a quantitative flux model to examine oxidative and reductive IDH flux in cancer cells grown in hypoxia and in cells with defective mitochondria. We analyze the lung cancer cell line A549 grown in hypoxia and the osteosarcoma cell line 143B-CYT B with a defective electron transport chain. In both cell types reductive IDH flux was recently claimed to have a central role in lipogenesis (10,11). We show that the observed fatty acid labeling from glutamine does not necessarily imply net reductive IDH flux. Indeed, by placing analytical bounds on the oxidative and reductive IDH fluxes based on metabolite isotope labeling, we find evidence for oxidative net flux in pseudohypoxia and for modest or no net flux in either direction in hypoxia. Thus, reductive IDH flux is not a major net contributor to acetyl-CoA production. Instead, cells cope with limited oxidative acetyl-CoA production by reducing the biosynthetic utilization of acetyl-CoA for fatty acid synthesis (23).

**Experimental Procedures**

Cell lines were grown in Dulbecco’s modified Eagle media (DMEM) without pyruvate (Cellgro), supplemented with 10% dialyzed fetal bovine serum (HyClone). Isogenic 143B human osteosarcoma cells that contained (143B-CYT B) or lacked (143B-WT) a loss-of-function mutation in mitochondrial complex III were grown in an incubator containing 5% CO2 and ambient oxygen at 37°C. For hypoxia experiments, A549 cells were grown inside a hypoxic chamber (Coy Lab) containing 1% oxygen and 5% CO2 at 37°C. For labeling experiments, medium was prepared from DMEM without glutamine (Cellgro), with the desired isotopic form of glutamine added to a final
concentration 0.584 g/l. Metabolite extractions were conducted at 70%-80% confluency.

For all metabolomic and isotope-tracer experiments, metabolism was quenched and metabolites extracted by quickly aspirating media and immediately adding -80°C 80:20 methanol: water extraction solution. Samples were analyzed for water soluble metabolites and saponified fatty acids by a stand-alone orbitrap mass spectrometer (Exactive) operating in negative ion mode was coupled to reversed-phase ion-pairing chromatography as previously described (23,24). In addition, confirmatory measurements of water soluble metabolites were acquired with a TSQ Quantum Discovery triple-quadrupole mass spectrometer operating in negative ion, multiple-reaction monitoring mode coupled to reverse-phase ion-pairing chromatography as described(25). Data were analyzed using the MAVEN software suite (26). Metabolite labeling patterns were adjusted for natural 13C abundance and for enrichment impurity of labeled substrate. Absolute metabolite levels were quantified as previously described (27), and normalized by packed cell volume. Acetate secretion rate was measured using the K-ACET kit (Megazyme) according to manufacturer's instructions. Oxygen consumption was measured by a Seahorse XF24 flux analyzer (Seahorse Bioscience, North Billerica, MA). To measure oxygen uptake in hypoxia, the Seahorse instrument was placed in the hypoxia chamber with 1% oxygen.

Results

Analysis of feasible IDH fluxes based on the experimentally observed acetyl-CoA labeling from [13C]-glutamine

While previous studies have shown that a major fraction of cytosolic acetyl-CoA gets labeled from [U-13C]-glutamine in hypoxia and pseudohypoxia, it is possible that oxidative IDH persists and exceeds the reductive flux. Here, we employ a simple isotopomer model to probe the feasible net IDH fluxes based on experimental measurements of TCA cycle influxes and effluxes (of α-ketoglutarate from glutamine and of 2-carbon units) and based on acetyl-CoA labeling from [U-13C]-glutamine.

Assuming pseudo steady-state for metabolite labeling, the isotopomer balance model shown in Figure 1 results in the following balance equation for citrate m+5:

\[ v3X_{akg5} = (v2 + v5)X_{cit5} \] (Eq. I)

and α-ketoglutarate m+5:

\[ v2X_{cit5} + v4 = (v3 + v6)X_{akg5} = (v2 + v4)X_{akg5} \] (Eq. II)

where \( X_{akg5} \) and \( X_{cit5} \) represent the fractional abundance of α-ketoglutarate m+5 and citrate m+5, respectively. The left hand side in both equations represents biosynthetic routes, while the right hand side represents consumption. Given experimental measurements of glutamine flux into TCA cycle via αKG (v4), acetyl-CoA demand for fatty acid biosynthesis (v5), labeling of citrate m+5, and unidirectional reductive IDH flux (v3), Equations I and II enable computation of net oxidative IDH flux (v2-v3). For simplicity, in this section, we assume zero labeling of mitochondrial acetyl-CoA from glutamine (i.e. negligible mitochondrial malic enzyme flux). This assumption tends to favor net flux in the reductive direction; hence, given our conclusions nevertheless show a propensity for net oxidative flux, it only strengthens them. Under this assumption, there is no contribution of citrate synthase to making citrate m+5 and the abundance of cytosolic acetyl-CoA m+2 equals that of citrate m+5.

Next, we applied this model to examine IDH fluxes in a lung cancer cell line A549 grown in hypoxia(10) and the osteosarcoma cell line 143B-CYTB having a defective electron transport chain and its isogenic wild-type cell line 143B (143B-WT)(11). Glutamine flux into TCA cycle (v4), as measured based on glutamine uptake rate from medium, minus glutamate and proline secretion, glutamine demand for protein biosynthesis, and dilution of glutamine and glutamate pools due to cell growth, was found to be 26-35 nmol/uL-cells/h across the three cell lines (Figure 2a).
To quantify the rate of acetyl-CoA demand for de novo fatty acid biosynthesis, we measured the total cellular fatty acid concentration (free and lipid-incorporated), the fraction of fatty acid that is de novo synthesized (measured by monitoring fatty acid labeling in cells fed with both [U-13C]-glucose and [U-13C]-glutamine), and cellular growth rate (23) (Figure 2b). Overall, the acetyl-CoA demand for fatty acid biosynthesis is 0.55-2.24 nmol/μL-cells/h across the three studied cell lines (Figure 2c).

To derive an upper bound on the additional acetyl-CoA demand for protein acetylation, we computed the acetyl-CoA requirement for acetylating all proteomic lysine residues (assuming that protein amounts to 50% of cellular weight and that the frequency of lysine is 5%), which is 0.5-0.9 nmol/μL-cells/h (Figure 2c). To examine whether an additional demand for acetyl-CoA exists due to protein acetylation and deacetylation cycling, we measured acetate secretion to the media (28). We find that in all three cell lines, acetate secretion is negligible (smaller than 0.02 nmol/μL-cells/h). Thus, to the extent that protein acetylation cycling occurs, it is not a major net consumer of 2C units.

Given these measurements of glutamine intake to TCA cycle (v4) and acetyl-CoA demand (v5) in 143B-CYTB, we applied Equations I and II to compute the IDH net flux, for various combinations of hypothetical cytosolic acetyl-CoA m+2 labeling and unidirectional reductive IDH flux (v3) (Figure 3a). We find that when feeding [U-13C] glutamine, for a given IDH net flux (v2-v3; which determines citrate synthase rate due to mass-balance considerations, as v1=v5-v2-v3), the fraction of acetyl-CoA m+2 increases as the reductive IDH flux (v3) increases, asymptotically reaching v4/(v4+v1) when the citrate and αKG pools are completely mixed. When IDH net flux is oxidative (v2>v3), mass-balance considerations entail that v1=v5, and hence the maximal fraction of acetyl-CoA m+2 is bounded by v4/(v4+v5), which is between 0.85 and 0.97 in the cell lines studied here (Figure 3b). To measure the actual cytosolic acetyl-CoA m+2 in these cell lines, we quantified fatty-acid labeling from [U-13C] glutamine by LC-MS (23) and used isotopomer spectral analysis (29). We find that in all cases, the fraction of cytosolic acetyl-CoA m+2 is substantially lower than the feasible upper bound consistent with net oxidative IDH flux. Thus net IDH flux in the oxidative direction is possible in all three cell lines (Figure 3b).

**Quantifying IDH oxidative and reductive flux via isotopic labeling of intracellular metabolites**

To determine the actual direction of net IDH flux, we derive analytical bounds on oxidative and reductive IDH flux based on experimentally observed metabolite steady-state labeling patterns. For this analysis, we no longer rely on the simplifying assumption of negligible labeling of mitochondrial acetyl-CoA from glutamine. Thus, we must account for citrate synthase potentially making citrate m+5. The resulting balance equation for citrate m+5 is:

\[ v3X_{akg5} + v1X_{mat3}X_{ac2} = (v2 + v5)X_{cit5} \]

(Eq. IV)

where \( X_{mat3} \) and \( X_{ac2} \) represent the fractional abundance of malate m+3 and mitochondrial acetyl-CoA m+2, respectively. Here, we assume rapid exchange between oxaloacetate and malate (which is easier to detect via LC-MS analysis) and hence a similar labeling pattern of both. Citrate m+5 whose only carbon #6 is unlabeled (denoted \( X_{cit5,Rc} \)) is made through reductive carboxylation of α-ketoglutarate m+5 and potentially through citrate synthase, depending on the positional labeling of malate m+3. Writing the balance equation for \( X_{cit5,Rc} \), while omitting the undetermined contribution of citrate synthase gives:

\[ v3X_{akg5} \leq X_{cit5,Rc}(v2 + v5) \]

(Eq. IV)

which combined with (III) (and assuming v1=v5-v2-v3 due to mass-balance considerations) gives the following lower bound on \( X_{cit5,Rc} \):

\[ X_{cit5} - X_{mat3} * X_{ac2} \leq X_{cit5,Rc} \]

(Eq. V)

The balance equation for α-ketoglutarate m+5 is

\[ v2(X_{cit5,Rc} + X_{cit5}) + v4 = (v3 + v6)X_{akg5} = (v2 + v4)X_{akg5} \]

(Eq. VI)
which gives:
\[ v_2 = v_4 \frac{1 - X_{Akgs}}{X_{Akgs} - X_{cit5,RC} - X_{cit6}} \]  
(Eq. VII)

Taking together Eq. (V) and (VII) give a lower bound on oxidative IDH flux (v2):
\[ v_2 \geq v_4 \frac{1 - X_{Akgs}}{X_{Akgs} - (X_{cit5} - X_{ma7}X_{ac2}) - X_{cit6}} \]  
(Eq. VIII)

This derivation relies on the fact that the fraction of cytosolic acetyl-CoA that is m+2 \((X_{ac2})\) exceeds that in the mitochondrion because cytosolic citrate (the source of cytosolic acetyl-CoA, assuming negligible acetyl-CoA synthetase activity since there is no acetate in the media) has only two sources: mitochondrial citrate (which will give equivalent labeling to the mitochondrion) or cytosolic α-ketoglutarate (which will give more labeling than the mitochondrion).

Since \(cit5,RC\) is a specific isotopomer of citrate m+5, its abundance, \(X_{cit5,RC}\), is no larger than \(X_{cit5}\). Hence, based on Equation VII, we get the following upper bound on \(v_2\):
\[ v_2 \leq v_4 \frac{1 - X_{Akgs}}{X_{Akgs} - X_{cit5} - X_{cit6}} \]  
(Eq. IX)

which combined with (III) gives an upper bound on reductive IDH flux (v3):
\[ v_3 \leq \left( v_4 \frac{1 - X_{Akgs}}{X_{Akgs} - X_{cit5} - X_{cit6}} + v_5 \right) \frac{X_{cit5}}{X_{Akgs}} \]  
(Eq. X)

To employ Equations VIII and X to derive bounds on the oxidative versus reductive IDH fluxes, we measured by LC-MS the labeling pattern of citrate, α-ketoglutarate, malate (Figure 4a). In both the wild-type and mitochondrial defective 143B cell lines, the oxidative IDH flux is significantly higher than the reductive flux, being at least 30-fold higher in 143B-WT and 2-fold higher in 143B-CYTB (Figure 4b). In A549 grown in hypoxia, the lower bound on oxidative IDH flux is roughly the same as the upper bound on the reductive flux, implying that there is at most modest net flux in the reductive direction (Figure 4b). Notably, considering the potential existence of other glutamine-consuming pathways not quantified here, glutamine flux into the TCA cycle may be overestimated in this study. However, as shown in Figure 4c, our results regarding no major IDH net flux still holds for substantially lower glutamine flux into TCA cycle via α-ketoglutarate.

**Mechanisms of redox and 2C-unit balancing in hypoxia and pseudohypoxia**

To assess how redox balancing is achieved in hypoxia without reductive IDH net flux, we measured the oxygen consumption in A549 and its fraction used by oxidative phosphorylation (using respiratory chain inhibition). We find that the oxygen consumption rate is \(~60\) nmol/μL-cells/h, which suffices to account for the observed oxidative TCA flux, given that glutamine flux to α-ketoglutarate is \(~35\) nmol/μL-cells/h and that glutamine is only partially oxidized in TCA cycle.

In 143B-CYTB, we find that redox balance is maintained by a branched TCA cycle activity, in which succinate is made both through the oxidation of acetyl-CoA and through the reduction of oxaloacetate. Specifically, the succinate secretion rate increases from a non-detected level in 143B to \(~11\) nmol/μL-cells/h in 143B-CYTB. Consistent with reductive production of succinate from oxaloacetate, we observed higher pyruvate carboxylase activity in 143B-CYTB, with unlabeled malate (in cells fed \([U-^{13}C]\)-glutamine and unlabeled glucose) increasing from 35% in 143B to 75% in 143B-CYTB.

These observations left open the question of how cells compensate for reduced acetyl-CoA production by pyruvate dehydrogenase in hypoxia. Based on recent evidence for increased fatty acid scavenging in hypoxia(23), we considered the possibility that this might serve to reduce 2C-unit demand. Indeed, quantitative analysis reveals that A549 cells in hypoxia decrease total 2C-unit consumption for fatty acid biosynthesis by 73% Moreover, reexamination of the fatty acid labeling patterns in Figure 2b revealed a large increase in the unlabeled fatty acid peak in cells fed with both \([U-^{13}C]\)-glucose and \([U-^{13}C]\)-glutamine in 143B-CYTB versus 143B-WT cells (i.e., in pseudohypoxia). Given that absolute total fatty acids concentrations are roughly the same in both
cell lines (e.g., palmitate is 18.7±1.0 and 15.1±2.6 nmol/uL-cells in 143B-WT and 143B-CYTB, respectively), the higher fraction of palmitate m+0 in 143B-CYTB implies enhanced fatty acid scavenging. Integrating across all experimentally measured fatty acids and accounting for cellular doubling time, we obtain a decrease in the 2C-unit requirement of 75%.

Discussion

Several recent studies have employed isotopic tracers to investigate how acetyl-CoA is produced in cancer cell lines in hypoxia and with defective mitochondria(10-13). Their conclusion was that acetyl-CoA is primarily made through reductive carboxylation of glutamine-derived α-ketoglutarate, suggesting potential therapeutic targets along this pathway for inhibiting hypoxic tumor growth. These studies followed previous reports of IDH reductive carboxylation flux in normal liver and cardiac cells (14-16). Here, we followed up on these studies and employed a quantitative flux model to analyze IDH flux in the same cancer cell lines. Our analysis shows that while reductive IDH flux indeed occurs in hypoxia and with mitochondrial deficiency, oxidative IDH flux persists, with net flux much less than flux in either direction.

A limitation of our analysis (as well as prior related analyses) is that it does not account for subcellular compartmentalization of most metabolites. For acetyl-CoA, we do account for the possibility of distinct labeling patterns in the mitochondria versus cytoplasm, using fatty acid labeling to infer cytosolic acetyl-CoA labeling. For other metabolites, the LC-MS approach employed here measures the isotopic labeling of the overall cellular pool, which may represent a mixture of different labeling patterns in distinct compartments (depending on the relative concentration of the metabolite in the various compartments and compartment volumes). Thus, we cannot rule out net reductive IDH flux in at least some compartments, e.g., if cytosolic and mitochondrial IDH are working in opposite directions, perhaps as a means for shuttling high energy electrons from mitochondria to cytoplasm (30,31).

Nevertheless, a simple mechanistic explanation for the observed labeling patterns involves simultaneous oxidative and reductive IDH flux due to near equilibrium between the isocitrate oxidation and α-ketoglutarate reductive carboxylation. Such bidirectional flux can result in extensive citrate and lipid labeling via reductive carboxylation without reductive IDH being a net contributor to citrate or acetyl-CoA production. In such cases net acetyl-CoA production may come from glucose or other carbon sources, with these influxes mixing with the larger TCA influx from glutamine via the reversible IDH reaction. The outcome is an apparent predominance of glutamine as the source of two-carbon units, despite net production coming from other sources.

More complete examination of fatty acid labeling patterns in hypoxia and pseudohypoxia reveals that glutamine labeling occurs in parallel with a rise in fatty acids that do not label from glucose or from glutamine. Such fatty acids are scavenged from media, and their assimilation into lipids decreases cellular requirements for 2C-unit production, thereby mitigating the need for either pyruvate dehydrogenase flux or reductive carboxylation.

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References:


Figures:

Figure 1: Network diagram

Figure 2: Glutamine intake to TCA cycle and acetyl-CoA demand. (a) Glutamine influx into TCA cycle inferred based on measurement of total glutamine uptake from media, minus glutamate and proline secretion, glutamine demand for protein biosynthesis, and dilution of glutamine and glutamate pools. (b) Labeling pattern of palmitate in 143B-WT and 143B-CYTB when fed with both [U-13C]-glucose and [U-13C]-glutamine. (c) Acetyl-CoA demand for fatty acid biosynthesis and protein acetylation.

Figure 3: Extensive labeling of acetyl-CoA from glutamine can occur without net reductive IDH flux. (a) Fraction of cytosolic acetyl-CoA m+2 labeling from [U-13C]-glutamine (y-axis) for various combinations of net IDH flux (represented by color) and unidirectional reductive IDH flux (x-axis) (fluxes shown in nmol/uL-cells/h). Oxidative IDH net flux is shown in blue, while reductive IDH net flux in green. The solid red line represents an upper bound on acetyl-CoA m+2 labeling when the net IDH flux is oxidative. The analysis was done based on measurements in 143B-CYTB. (b) Measured acetyl-CoA m+2 labeling (blue) versus the feasible upper bound (red) assuming oxidative IDH net flux.

Figure 4: Bounding oxidative and reductive IDH fluxes via steady-state metabolite labeling patterns. (a) Measured fractional labeling of α-ketoglutarate m+5, citrate m+5, and malate m+3 from [U-13C]-glutamine. (b) A lower bound on IDH oxidative flux (blue) versus upper bound on IDH reductive flux (red) calculated based on Equations VIII and X. (c) Lower bound on IDH net flux (calculated by subtracting the upper bound on IDH reductive flux from the lower bound on IDH oxidative flux), assuming potentially lower glutamine flux into TCA cycle via α-ketoglutarate (v4). The lower bound on net oxidative IDH flux is marked with a straight line while the standard deviation is marked with a dashed line.
Figure 1:


CO₂

Malate → Succinate → AKG → Glutamine

v1, v2, v3, v4, v5, v6
Figure 2:
Figure 3:

(a) 

(b) 

[Graph depicting hypothetical acetyl-CoA m2 labeling from [U-13C]glutamine vs hypothetical reductive IDH flux (v3) [nmol/ul-cells/h].]

[Bar chart showing Acetyl-CoA m2 labeling from [U-13C]glutamine for 143B-WT, 143B-CYT8, and A549.]
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