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***MET*abolic Adaptations in the Tumor *MYC*roenvironment**

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In this issue of *Cell Metabolism*, Yuneva et al. (2012) use mouse cancer models to characterize tumor nutrient metabolism in vivo. This study suggests that the metabolic phenotype of cancer cells is not only determined by the mutational status of specific oncogenes but is also influenced by the cell of origin and tumor micro-environment.

Cancer cells exhibit metabolic alterations to support aberrant tissue growth. Evidence from in vitro cancer models suggests that many tumor cells utilize aerobic glycolysis, while some metabolize high amounts of the amino acid glutamine (Cairns et al., 2011). Different metabolic phenotypes in cell lines have been attributed to specific genetic events associated with cancer; however, there is a paucity of evidence exploring whether the same relationships between genotype and phenotype persist in vivo. Yuneva et al. (2012) evaluate metabolic changes in tumors arising in genetically engineered mouse models to show that the tissue of origin, even in the presence of the same activating oncogenic mutation, can differentially influence the metabolic rewiring of tumor cells (Figure 1).

Many oncogenic events, including constitutive expression of *MYC* or *MET*, influence cell metabolism. Enzymes involved in glucose uptake, lactate excretion, and glutamine catabolism are important targets of Myc regulation, and it has been suggested that Myc can addict cells to specific bioenergetic substrates (Wise and Thompson, 2010). *MET* activates the PI3K/Akt, RAS/MAPK, and Wnt/ β -catenin signaling pathways (Trusolino et al., 2010), and these signaling pathways impact metabolic pathway regulation through a variety of mechanisms (Cairns et al., 2011).

Yuneva et al. (2012) examine whether tumors initiated by either *MYC* or *MET* expression exhibit elevated glucose consumption with lactate production (the “Warburg effect”). By following labeled glucose fate, the authors observed increased glucose catabolism across all

tumors profiled. Increased lactate production relative to control tissues was observed in *MYC*-induced liver and lung tumors, but not in *MET*-induced liver tumors despite increased lactate dehydrogenase (*Ldha*) expression in all three tissues. These findings demonstrate that increased glucose to lactate conversion is not a feature of all cancers. They also illustrate that changes in enzyme expression are not necessarily predictive of a metabolic phenotype. Nevertheless, the *MYC*-induced liver tumors had elevated glucose uptake relative to the *MET*-induced liver tumors as measured by FDG-PET, suggesting that increased lactate correlates with glucose uptake in vivo. Together, these results suggest that cancer cells utilize different metabolic programs to support tumor growth.

Numerous studies have demonstrated that Myc can promote glutamine metabolism in cells (Wise and Thompson, 2010). *SLC1A5*, a major transporter for glutamine uptake, is upregulated following oncogenic Myc expression, and c-Myc suppresses the microRNA miR23a/b to promote glutaminase (Gls) expression and glutamine consumption (Gao et al., 2009). Both glutamine and glutamate are important nitrogen sources for anabolic metabolism, but in many cells glutamine is consumed in excess of this nitrogen requirement (DeBerardinis et al., 2007). This is explained at least in part by the metabolism of glutamine-derived carbon to fuel the tricarboxylic acid (TCA) cycle and support mitochondrial ATP production as well as to supply important precursors for biosynthesis (Metallo et al., 2011; Wise and Thompson, 2010). The exact role glutamine metabolism plays in cancer

cells is still debated and is likely context dependent; however, it is clear that many cancer cells require glutamine for growth.

The glutamine-tracing experiments performed in this study underscore the importance of glutamine catabolism by tumors, but also show that glutamine can be synthesized by cancers. Some cell lines can grow in the absence of glutamine, and the endogenous production of glutamine implies that this may also be the case for some cancer cells in vivo. Low tumor glutamine levels with increased labeling of TCA cycle intermediates from ¹³C-labeled glutamine were observed in *MYC*-induced liver tumors. This finding matches the increased expression of *Slc1A5* and *Gls* together with repression of glutamine synthetase (*Glu1*) in these tumors. It is also consistent with tissue culture studies arguing that *MYC* expression controls expression of *Slc1A5* and *Gls* to promote dependence on exogenous glutamine, while *MYC*-overexpressing cells undergo apoptosis when glutamine is absent (Wise and Thompson, 2010). In contrast, the *MET*-induced liver tumors expressed *Glu1* and had low *Gls* levels. This is consistent with endogenous glutamine production, and these tumors had increased labeled glutamine from ¹³C-labeled glucose. Strikingly, *Glu1* expression was also increased in the *MYC*-induced lung tumors, and these tumors had elevated levels of glutamine compared to normal tissue. *Glu1* is regulated by β -catenin, and therefore possibly by Met, but is not a known Myc target. Therefore, the authors hypothesize that *Glu1* expression may be secondary to an inflammatory

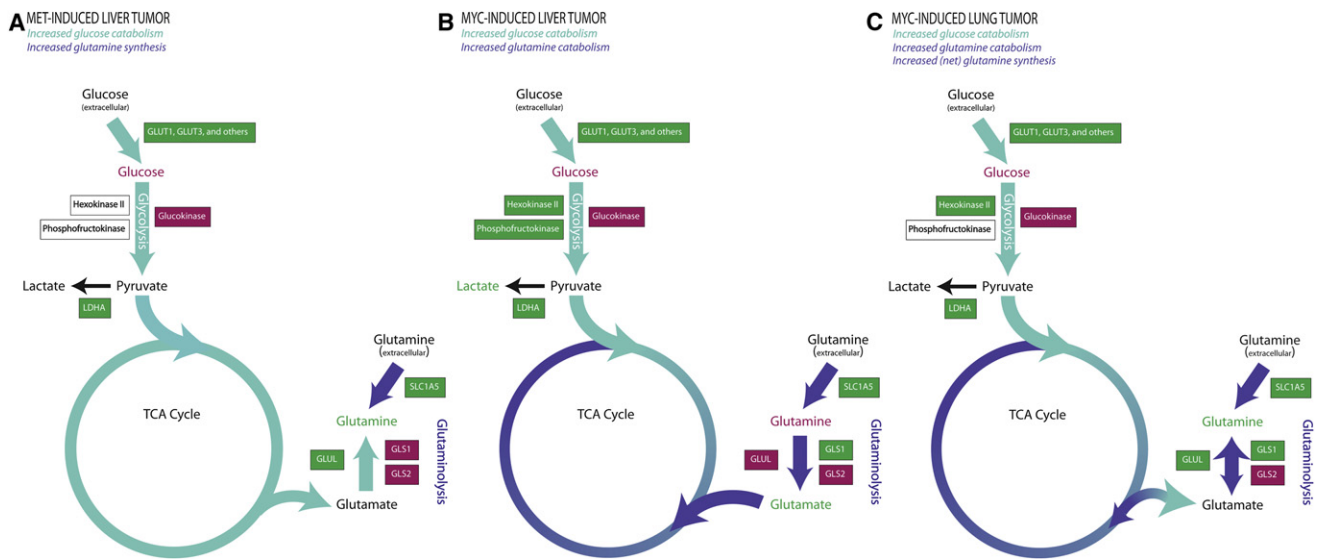


Figure 1. Functional Analysis of Metabolism Is Necessary to Reveal the Metabolic Heterogeneity of Tumors

(A) Liver tumors induced by MET have increased glucose uptake but despite increased *Ldha* expression show no increase in lactate levels. Net glutamine synthesis is observed along with downregulation of *Gls2* and upregulation of *Glul*.
 (B) Like MET-induced liver tumors, MYC-induced liver tumors also exhibit increased glucose uptake. However, in these tumors increased *Ldha* expression is associated with increased lactate production. In addition, these tumors use glutamine to fuel the citric acid cycle.
 (C) MYC-induced lung tumor metabolism resembles MET-induced liver tumor metabolism, with apparent net glutamine synthesis resulting from increased *Glul* expression. While it is likely these tumors still consume glutamine, glutamine levels are high, suggesting that glutamine synthesis outpaces consumption. Green, upregulated compared to control tissue at the level of transcription, translation, or metabolite levels. Red, downregulated compared to control tissue at the level of transcription, translation, or metabolite levels. Black, no change in enzyme/metabolite levels compared to control tissue, or the enzyme/metabolite was not explicitly examined.

microenvironment in the tumor. If true, this effect must be dominant over the Myc effect on glutamine metabolism.

Taken together, this evaluation of metabolism in different tumor types suggests that the metabolic program of cancer cells in vivo is determined by multiple factors, and neither the tissue of origin and associated microenvironment nor the presence of a single genetic driver event is sufficient to define the metabolic phenotype. The data also argue that MYC-driven tumor cells may have a variable dependence on glutamine metabolism for growth and survival in vivo. The authors show high expression of *Gls1* protein in MYC-induced lung tumor cells, and it is possible that these cells remain dependent on glutamine catabolism even though the cells are producing glutamine in excess of consumption. Furthermore, MYC-induced lung cancers do not fully regress following MYC inactivation, implying a decreased role for Myc in tumor maintenance (Tran et al., 2008). Incomplete regression following MYC inactivation is also observed in a MYC-driven breast cancer model (Boxer et al., 2004), and studies of these tumors could inform whether differences in glutamine

metabolism are a marker of MYC dependence in vivo.

Low and variable enrichment of the ^{13}C -isotopic tracers was observed compared with unlabeled glucose and glutamine, and as a result only the most abundantly labeled metabolites were detectable. In addition, because it is unlikely that steady-state concentrations of labeled substrates were provided to tumors, quantitative metabolic flux analysis or analogous approaches to model metabolic states are limited. Delivering higher percentages of label over a prolonged period will allow for further elucidation of relevant metabolic differences that exist among tumor cells in vivo. Dynamic nuclear polarization of ^{13}C tracers with magnetic resonance spectroscopic imaging (MRSI) has also been used to characterize metabolic changes associated with de novo tumor formation in c-Myc-induced liver tumors (Hu et al., 2011). Similar to Yuneva et al. (2012), this study found increased lactate production in MYC-driven liver tumors. In addition, Hu et al. found increased conversion of pyruvate to alanine as a hallmark of MYC-dependent tumor initiation,

illustrating that use of multiple modalities to characterize tumor metabolism is another way to gain insight. Nevertheless, this study provides an important caution that cell culture models do not reflect all the complexities of cancer metabolism that exist in autochthonous tumors. Understanding how cell of origin, tumor microenvironment, and genetic events cooperate to define a metabolic phenotype that allows tumor growth and survival is critical to effectively target cell metabolism to benefit cancer patients.

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Neuron Transplantation Partially Reverses an Obesity Disorder in Mice

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Mice lacking leptin receptors are grossly obese and diabetic, in part due to dysfunction in brain circuits important for energy homeostasis. Transplantation of leptin receptor-expressing hypothalamic progenitor neurons into the brains of leptin receptor deficient mice led to integration into neural circuits, reduced obesity, and normalized circulating glucose levels.

Neuron transplantation has been explored as a treatment for debilitating conditions, including Parkinson's disease, blindness, and stroke. In *Science*, Czupryn et al. (2011) report the capacity of neural transplantation to reverse the consequences of a genetic defect in leptin signaling. This study shows that obesity and diabetes in mice lacking the leptin receptor can be partially reversed after transplanting hypothalamic cells from mice with functional leptin receptors.

The hormone leptin (Zhang et al., 1994) is produced by adipose tissue and broadcasts energetic status to the rest of the body. Previous work has demonstrated that leptin receptor expression in neurons is essential for preventing obesity (Cohen et al., 2001). Moreover, leptin receptor expression in specific classes of neurons rescues discrete aspects of energy homeostasis in leptin receptor null (*db/db*) mice (Kowalski et al., 2001). Czupryn et al. pursued a creative approach to examine the development and function of leptin-sensitive neural circuits. They used ultrasound-guided microtransplantation to graft leptin receptor expressing neurons into the hypothalamus of newborn *db/db* mice. The researchers asked three main questions: (1) Would

transplanted neural progenitors differentiate into regionally appropriate neuron classes? (2) Would transplanted neurons incorporate into neural circuits with host neurons? (3) Would the metabolic phenotype associated with the *db* mutation be affected by transplantation of a small number of leptin receptor-expressing cells?

To address the first two questions, the researchers transplanted cells carrying a green fluorescent protein transgene, which allowed them to be identified for analysis and compared to surrounding host cells. Hypothalamic grafts differentiated into electrophysiologically and histochemically determined neuronal cell types that were consistent with previously characterized hypothalamic populations. Donor cells integrated into local circuits by receiving functional synaptic connections. Importantly, some of the transplanted cells were leptin responsive. Analysis of metabolic parameters showed that *db/db* mice with hypothalamic grafts had a nearly 20% reduction in body weight relative to mice with mock transplantation or cortical progenitor grafts in the hypothalamus. This effect was apparently due to an increase in energy expenditure because food intake remained elevated.

Most strikingly, basal blood glucose was normalized to wild-type levels, although insulin levels remained high. These interesting results suggest multiple directions for neuronal transplantation to be used to probe principles of hypothalamic development and function. In addition, the technique is of interest as a possible strategy for treating obesity.

Neuronal transplantation offers a method to determine regional and temporal requirements for cell-type specification (Gaiano and Fishell, 1998). The hypothalamus is composed of a large number of intermingled, molecularly defined cell types with different functions that are grouped regionally into brain "nuclei." Judging by the electrophysiological characteristics that the authors report, the results are mostly consistent with regionally appropriate differentiation. At a molecular level, though, this is less clear. For instance, POMC and NPY neurons were found in the grafts, but it was not shown whether the differentiation of POMC and NPY neurons was limited to the arcuate nucleus, which is their location in the hypothalamus. The methods highlighted in this study could be further applied to investigate cell-type specification in the hypothalamus.