Metastatic melanoma is a metabolic disease; plasma levels of lactate dehydrogenase isoenzymes (LDH) catalyze the conversion of pyruvate, the major product of glycolytic metabolism to lactate—correlate with melanoma prognosis and are in fact incorporated into its staging system (1). More recently in the era of targeted therapy, dramatic changes in glucose uptake upon pharmacologic treatment of patients with metastatic melanoma have demonstrated that current generation therapies lead to rapid changes in tumor metabolism, often before observable tumor regression. It is essential to elucidate whether these metabolic phenomena are mere consequences of the oncogenic process or, more significantly, essential drivers of tumorigenesis. Improved understanding of the functional role of these changes may enable identification of rational approaches to target metabolic vulnerabilities.

Disregulation of metabolism in cancer is related to the acquisition of genetic changes in metabolic genes and regulatory pathways. In melanoma, the most common genetic alterations are activating mutations in the BRAF proto-oncogene. Roughly half of melanomas have substitution of valine at position 600 by glutamic acid (BRAFV600E), which results in the constitutive activation of its serine/threonine kinase activity and sustained activation of the mitogen-activated protein kinase (MAPK) signal transduction pathway (2). Recently, a downstream target of oncogenic BRAF, the melanocyte lineage factor microphthalmia (MITF), was found to be critical in reprogramming metabolism through its direct actions on the mitochondrial master regulator, PGC1α (3). BRAF suppressed oxidative phosphorylation by modulating MITF and PGC1α levels, whereas inhibition of BRAF, which temporally suppresses melanoma growth in vitro and in patients, induced PGC1α and oxidative phosphorylation. Therefore, melanomas treated with BRAF-targeted therapy become addicted to oxidative phosphorylation, which suggests that mitochondrial inhibitors may be useful in combination with BRAF pathway inhibitors.

In this issue of Cancer Discovery, Parmenter and colleagues (4) further our understanding of the metabolic consequences of oncogenic mutations in BRAF by providing novel mechanistic insight and suggesting other therapeutic opportunities. In particular, the authors demonstrate that inhibition of BRAF leads to decreases in glucose uptake both in cell culture and in patients with melanoma. These metabolic changes correlated with suppression of MAPK signaling and were restored in patients who developed resistance to BRAF inhibitors. To investigate the pathways by which BRAF regulates glycolysis, the authors performed microarray gene expression analysis of several melanoma cell lines following treatment with BRAF inhibitors. They identified a network of BRAF-regulated transcription factors that control glycolysis in melanoma cells, including hypoxia-inducible factor-1α (HIF-1α), c-MYC, and MONDOA. Knockdown of c-MYC or HIF-1α inhibited glucose uptake, similar to BRAF inhibition. c-MYC and HIF-1α modulated levels of the GLUT family of glucose transporters, as well as the expression of hexokinase 2 (which regulates the first step in the glycolytic pathway). The authors finally demonstrate that these transcriptional targets were functionally important in the effects of BRAF inhibitors on glycolysis and cell proliferation.

How can the results of this study be used to improve treatment of patients with metastatic melanoma? Targeting metabolic targets is likely to be challenging, though one approach suggested involves inhibiting the described BRAF–HIF-1α pathway. HIF-1α is known to promote glycolysis in part by inducing the expression of pyruvate dehydrogenase kinase (PDH), a negative regulator of pyruvate dehydrogenase (PDH; refs. 5–7). Through these actions, HIF-1α inhibits the entry of pyruvate into the tricarboxylic acid (TCA) cycle. The authors show that pyruvate mimetics, such as dichloroacetate (DCA), decrease lactate production (presumably through oxidative metabolism of pyruvate) and synergistically enhance cytotoxicity of BRAF inhibitors in vitro. Although DCA is available in the clinic to treat lactic acidosis, dose-dependent toxicities have limited its use in a glioblastoma clinical trial (8).
Nonetheless, the combination of DCA (or newer generation mimetics) with BRAF pathway inhibitors may be a reasonable approach to target this crucial metabolic pathway.

The use of PDK (or HIF-1α) inhibitors is likely to be a double-edged sword. The most obvious danger is augmenting mitochondrial function that in some cases may support the bioenergetic demands of the melanoma cells (3). DCA has been shown to alter mitochondria when given to patients in clinical trials. In fact, the authors show that vemurafenib and DCA treatment of melanoma cells in vitro led to increased mitochondrial respiration as well as the production of reactive oxygen species (ROS). ROS is a byproduct of mitochondrial respiration during electron transfer to oxygen. Is the synergy between vemurafenib and DCA related to effects on glycolysis or, instead, due to toxic levels of ROS in the cells studied? Clarification may further instruct the development of combinatorial therapies and general applicability of these findings.

Alternative approaches to target the glycolytic metabolism of melanomas ought to be explored. Hexokinase 2, a target of BRAF signaling identified by the authors through its actions on c-MYC, is essential for glycolysis. Hexokinase converts glucose to glucose-6-phosphate. Hexokinase can be competitively inhibited by the drug 2-deoxyglucose (2-DG), producing the inactive metabolite deoxyglucose-6-phosphate. Although 2-DG has been evaluated in clinical trials, its numerous cardiac side effects may preclude its use as a cancer therapeutic. However, specific inhibition of the hexokinase 2 isoform may be an approach to selectively target tumors, as this isoform seems especially critical in tumors but not in normal tissues (9).

How BRAF regulates HIF-1α and c-MYC is not addressed by this study. The transcriptional changes occur independently of the effects of BRAF inhibition on cell cycle and apoptosis. Surprisingly, the authors show that the effect of BRAF inhibition does not involve the phosphoinositide 3-kinase (PI3K) or mTOR signaling pathways, which are known regulators of glycolysis. Further work will require delineation of these pathways, as they too may be attractive therapeutic targets. Although these studies were conducted in melanoma, the generality of the findings in other cancer types also warrants exploration.

Like other approaches to target melanoma, such as chemotherapy or targeted therapy, the success of metabolic targeting may also be limited by the development of acquired or adaptive resistance mechanisms, such as glutamine metabolism or oxidative phosphorylation. However, the results of Parmenter and colleagues (4) and other recent data (3, 10) suggest that oncogenic BRAF (and MAPK) may have greater roles in metabolism than previously realized. The growing appreciation for the metabolic networks that are regulated by BRAF suggests that tumorigenesis associated with oncogenic BRAF is critically dependent on dysregulated metabolism. Deep mechanistic understanding of these phenomena, it is hoped, may well instruct the next generation of therapies for our patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Metabolic Dysregulation in Melanoma: Cause or Consequence?

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