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Cancer Cell Metabolism: Warburg and Beyond

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Described decades ago, the Warburg effect of aerobic glycolysis is a key metabolic hallmark of cancer, yet its significance remains unclear. In this Essay, we re-examine the Warburg effect and establish a framework for understanding its contribution to the altered metabolism of cancer cells.

It is hard to begin a discussion of cancer cell metabolism without first mentioning Otto Warburg. A pioneer in the study of respiration, Warburg made a striking discovery in the 1920s. He found that, even in the presence of ample oxygen, cancer cells prefer to metabolize glucose by glycolysis, a seeming paradox as glycolysis, when compared to oxidative phosphorylation, is a less efficient pathway for producing ATP (Warburg, 1956). The Warburg effect has since been demonstrated in different types of tumors and the concomitant increase in glucose uptake has been exploited clinically for the detection of tumors by fluorodeoxyglucose positron emission tomography (FDG-PET). Although aerobic glycolysis has now been generally accepted as a metabolic hallmark of cancer, its causal relationship with cancer progression is still unclear. In this Essay, we discuss the possible drivers, advantages, and potential liabilities of the altered metabolism of cancer cells (Figure 1). Although our emphasis on the Warburg effect reflects the focus of the field, we would also like to encourage a broader approach to the study of cancer metabolism that takes into account the contributions of all interconnected small molecule pathways of the cell.

The Tumor Microenvironment Selects for Altered Metabolism

One compelling idea to explain the Warburg effect is that the altered metabolism of cancer cells confers a selective advantage for survival and proliferation in the unique tumor microenvironment. As the early tumor expands, it outgrows the diffusion limits of its local blood supply, leading to hypoxia and stabilization of the hypoxia-inducible transcription factor, HIF. HIF initiates a transcriptional program that provides multiple solutions to hypoxic stress (reviewed in Kaelin and Ratcliffe, 2008). Because a decreased dependence on aerobic respiration becomes advantageous, cell metabolism is shifted toward glycolysis by the increased expression of glycolytic enzymes, glucose transporters, and inhibitors of mitochondrial metabolism. In addition, HIF stimulates angiogenesis (the formation of new blood vessels) by upregulating several factors, including most prominently vascular endothelial growth factor (VEGF).

Blood vessels recruited to the tumor microenvironment, however, are disorganized, may not deliver blood effectively, and therefore do not completely alleviate hypoxia (reviewed in Gatenby and Gillies, 2004). The oxygen levels within a tumor vary both spatially and temporally, and the resulting rounds of fluctuating oxygen levels potentially select for tumors that constitutively upregulate glycolysis. Interestingly, with the possible exception of tumors that have lost the von Hippel-Lindau protein (VHL), which normally mediates degradation of HIF, HIF is still coupled to oxygen levels, as evident from the heterogeneity of HIF expression within the tumor microenvironment (Wiesener et al., 2001; Zhong et al., 1999). Therefore, the Warburg effect—that is, an uncoupling of glycolysis from oxygen levels—cannot be explained solely by upregulation of HIF. Other molecular mechanisms are likely to be important, such as the metabolic changes induced by oncogene activation and tumor suppressor loss.

Oncogene Activation Drives Changes in Metabolism

Not only may the tumor microenvironment select for a deranged metabolism, but oncogene status can also drive metabolic changes. Since Warburg's time, the biochemical study of cancer metabolism has been overshadowed by efforts to identify the mutations that contribute to cancer initiation and progression. Recent work, however, has demonstrated that the key components of the Warburg effect—increased glucose consumption, decreased oxidative phosphorylation, and accompanying lactate production—are also distinguishing features of oncogene activation. The signaling molecule Ras, a powerful oncogene when mutated, promotes glycolysis (reviewed in Dang and Semenza, 1999; Ramanathan et al., 2005). Akt kinase, a well-characterized downstream effector of insulin signaling, reprises its role in glucose uptake and utilization in the cancer setting (reviewed in Manning and Cantley, 2007), whereas the Myc transcription factor upregulates the expression of various metabolic genes (reviewed in Gordan et al., 2007). The most parsimonious route to tumorigenesis may be activation of key oncogenic nodes that execute a proliferative program, of which metabolism may be one important arm. Moreover, regulation of metabolism is not exclusive to oncogenes. Loss of the tumor suppressor protein p53 prevents expression of

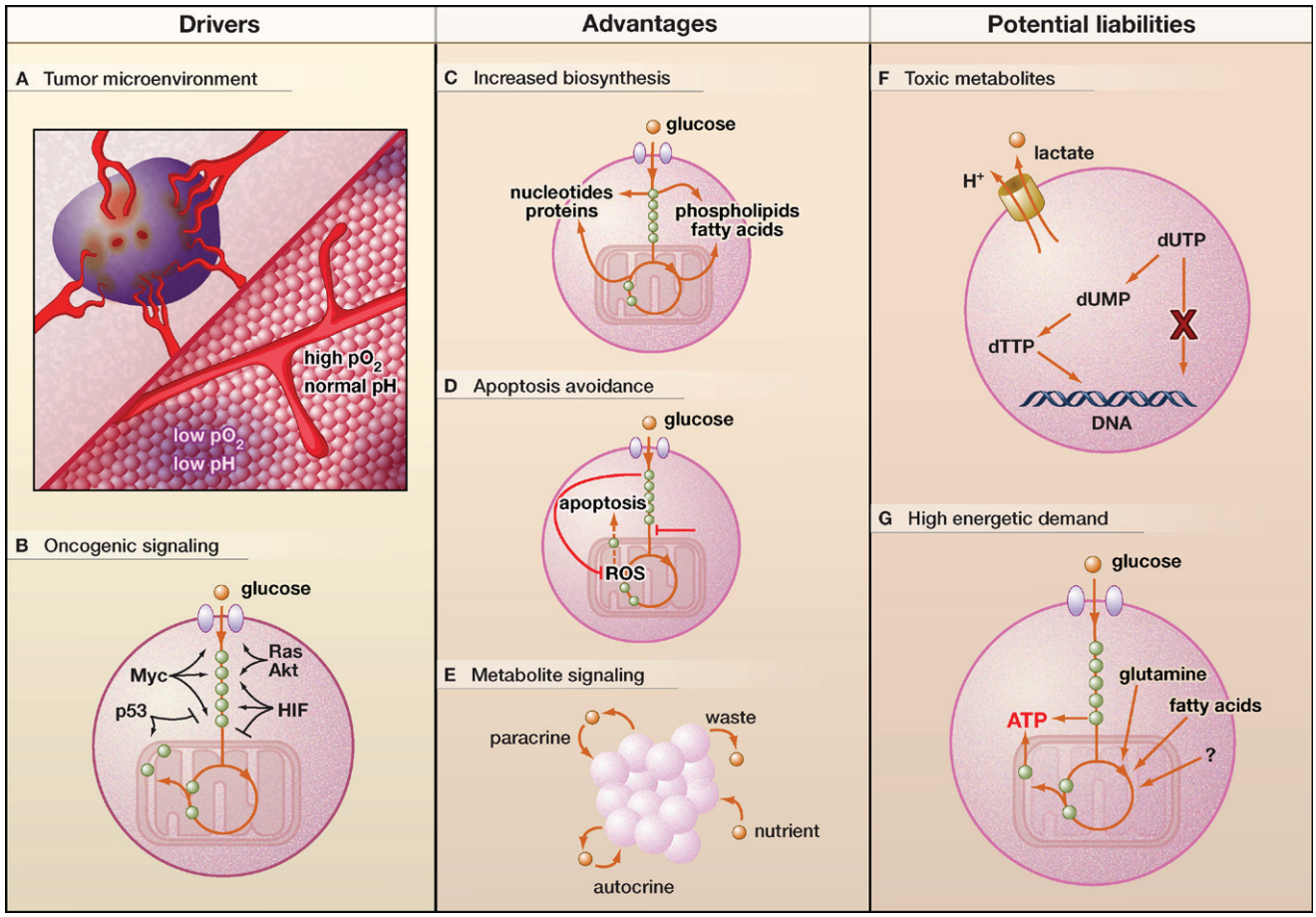

Figure 1. The Altered Metabolism of Cancer Cells

Drivers (A and B). The metabolic derangements in cancer cells may arise either from the selection of cells that have adapted to the tumor microenvironment or from aberrant signaling due to oncogene activation. The tumor microenvironment is spatially and temporally heterogeneous, containing regions of low oxygen and low pH (purple). Moreover, many canonical cancer-associated signaling pathways induce metabolic reprogramming. Target genes activated by hypoxia-inducible factor (HIF) decrease the dependence of the cell on oxygen, whereas Ras, Myc, and Akt can also upregulate glucose consumption and glycolysis. Loss of p53 may also recapitulate the features of the Warburg effect, that is, the uncoupling of glycolysis from oxygen levels.

Advantages (C–E). The altered metabolism of cancer cells is likely to imbue them with several proliferative and survival advantages, such as enabling cancer cells to execute the biosynthesis of macromolecules (C), to avoid apoptosis (D), and to engage in local metabolite-based paracrine and autocrine signaling (E).

Potential Liabilities (F and G). This altered metabolism, however, may also confer several vulnerabilities on cancer cells. For example, an upregulated metabolism may result in the build up of toxic metabolites, including lactate and noncanonical nucleotides, which must be disposed of (F). Moreover, cancer cells may also exhibit a high energetic demand, for which they must either increase flux through normal ATP-generating processes, or else rely on an increased diversity of fuel sources (G).

the gene encoding SCO2 (the synthesis of cytochrome *c* oxidase protein), which interferes with the function of the mitochondrial respiratory chain (Matoba et al., 2006). A second p53 effector, TIGAR (TP53-induced glycolysis and apoptosis regulator), inhibits glycolysis by decreasing levels of fructose-2,6-bisphosphate, a potent stimulator of glycolysis and inhibitor of gluconeogenesis (Bensaad et al., 2006). Other work also suggests that p53-mediated regulation of glucose metabolism may be dependent on the transcription factor NF-κB (Kawauchi et al., 2008).

It has been shown that inhibition of lactate dehydrogenase A (LDH-A) prevents the Warburg effect and forces cancer cells to revert to oxidative phosphorylation in order to reoxidize NADH and produce ATP (Fantin et al., 2006; Shim et al., 1997). While the cells are respiratory competent, they exhibit attenuated tumor growth, suggesting that aerobic glycolysis might be essential for cancer progression. In a primary fibroblast cell culture model of stepwise malignant transformation through overexpression of telomerase, large and small T antigen, and the H-Ras oncogene, increasing tumorigenicity correlates with sensitivity to glycolytic inhibition. This finding suggests that the Warburg effect might be inherent to the molecular events of transformation (Ramanathan et al., 2005). However, the introduction of similar defined factors into human mesenchymal stem cells (MSCs) revealed that transformation can be associated with increased dependence on oxidative phosphorylation (Funes et al., 2007). Interestingly, when introduced in vivo these transformed MSCs do upregulate glycolytic genes, an effect that is reversed when the cells are explanted and cultured under normoxic conditions.

These contrasting models suggest that the Warburg effect may be context dependent, in some cases driven by genetic changes and in others by the demands of the microenvironment. Regardless of whether the tumor microenvironment or oncogene activation plays a more important role in driving the development of a distinct cancer metabolism, it is likely that the resulting alterations confer adaptive, proliferative, and survival advantages on the cancer cell.

Altered Metabolism Provides Substrates for Biosynthetic Pathways

Although studies in cancer metabolism have largely been energy-centric, rapidly dividing cells have diverse requirements. Proliferating cells require not only ATP but also nucleotides, fatty acids, membrane lipids, and proteins, and a reprogrammed metabolism may serve to support synthesis of macromolecules. Recent studies have shown that several steps in lipid synthesis are required for and may even actively promote tumorigenesis. Inhibition of ATP citrate lyase, the distal enzyme that converts mitochondrial-derived citrate into cytosolic acetyl coenzyme A, the precursor for many lipid species, prevents cancer cell proliferation and tumor growth (Hatzivassiliou et al., 2005). Fatty acid synthase, expressed at low levels in normal tissues, is upregulated in cancer and may also be required for tumorigenesis (reviewed in Menendez and Lupu, 2007). Furthermore, cancer cells may also enhance their biosynthetic capabilities by expressing a tumor-specific form of pyruvate kinase (PK), M2-PK. Pyruvate kinase catalyzes the third irreversible reaction of glycolysis, the conversion of phosphoenolpyruvate (PEP) to pyruvate. Surprisingly, the M2-PK of cancer cells is thought to be less active in the conversion of PEP to pyruvate and thus less efficient at ATP production (reviewed in Mazurek et al., 2005). A major advantage to the cancer cell, however, is that the glycolytic intermediates upstream of PEP might be shunted into synthetic processes. Recent work has found that the cancer-specific M2-PK causes an increase in the incorporation of glucose carbons into lipids and, expanding the connection between growth factor signaling and cancer metabolism, may be regulated by phosphotyrosine binding (Christofk et al., 2008a, 2008b).

Making the building blocks of the cell, however, incurs an energetic cost and cannot fully explain the Warburg effect. Biosynthesis, in addition to causing an inherent increase in ATP demand in order to execute synthetic reactions, should also cause a decrease in ATP supply as various glycolytic and Krebs cycle intermediates are diverted. Lipid synthesis, for example, requires the cooperation of glycolysis, the Krebs cycle, and the pentose phosphate shunt. As pyruvate must enter the mitochondria in this case, it avoids conversion to lactate and therefore cannot contribute to glycolysis-derived ATP. Moreover, whereas increased biosynthesis may explain the glucose hunger of cancer cells, it cannot explain the increase in lactic acid production originally described by Warburg, suggesting that lactate must also result from the metabolism of non-glucose substrates. Recently, it has been demonstrated that glutamine may be metabolized by the citric acid cycle in cancer cells and converted into lactate, producing NADPH for lipid biosynthesis and oxaloacetate for replenishment of Krebs cycle intermediates (DeBerardinis et al., 2007).

Metabolic Pathways Regulate Apoptosis

In addition to involvement in proliferation, altered metabolism may promote another cancer-essential function: the avoidance of apoptosis. Loss of the p53 target TIGAR sensitizes cancer cells to apoptosis, most likely by causing an increase in reactive oxygen species (Bensaad et al., 2006). On the other hand, overexpression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) prevents caspase-independent cell death, presumably by stimulating glycolysis, increasing cellular ATP levels, and promoting autophagy (Colell et al., 2007). Whether or not GAPDH plays a physiological role in the regulation of cell death remains to be determined.

Intriguingly, Bonnet et al. (2007) have reported that treating cancer cells with dichloroacetate (DCA), a small molecule inhibitor of pyruvate dehydrogenase kinase, has striking effects on their survival and on xenograft tumor growth. DCA, a currently approved treatment for congenital lactic acidosis, activates oxidative phosphorylation and promotes apoptosis by two mechanisms. First, increased flux through the electron transport chain causes depolarization of the mitochondrial membrane potential (which the authors found to be hyperpolarized specifically in cancer cells) and release of the apoptotic effector cytochrome *c*. Second, an increase in reactive oxygen species generated by oxidative phosphorylation upregulates the voltage-gated K^+ channel, leading to potassium ion efflux and caspase activation. Their work suggests that cancer cells may shift their metabolism to glycolysis in order to prevent cell death and that forcing cancer cells to respire aerobically can counteract this adaptation. Although this preliminary work has prompted some cancer patients to self-medicate with DCA, a controlled clinical trial will be essential to demonstrate unequivocally the safety and efficacy of DCA as an anti-cancer agent.

Cancer Cells May Signal Locally in the Tumor Microenvironment

Cancer cells may rewire metabolic pathways to exploit the tumor microenvironment and to support cancer-specific signaling. Without access to the central circulation, it is possible that metabolites can be concentrated locally and reach suprasystemic levels, allowing cancer cells to engage in metabolite-mediated autocrine and paracrine signaling that does not occur in normal tissues. So-called androgen-independent prostate cancers may only be independent from exogenous, adrenal-synthesized androgens. Androgen-independent prostate cancer cells still express the androgen receptor and may be capable of autonomously synthesizing their own androgens (Stanbrough et al., 2006).

Perhaps the more provocative but as yet untested idea is that metabolites in the diffusion-limited tumor microenvironment could be acting as paracrine signaling molecules. Traditionally thought of as a glycolytic waste product, lactate may be one such signal. As noted above, it has been found that inhibition of lactate dehydrogenase can block tumor growth, most likely by multiple mechanisms. Much of the evidence for lactate as a multifunc-

tional metabolite comes from work in exercise physiology and muscle metabolism (reviewed in Philp et al., 2005). Transported by several monocarboxylate transporters, lactate may be shared and metabolized among cells, although the idea is still controversial (Hashimoto et al., 2006; Yoshida et al., 2007). The interconversion of lactate and pyruvate might alter the NAD^+/NADH ratio in cells, and lactate exchange may serve to coordinate the metabolism of a group of cells. The tumor-stroma interaction may therefore have a metabolic component (Koukourakis et al., 2006). Cancer cells respond cell-autonomously to hypoxia to initiate angiogenesis, and so it would be exciting if a metabolite such as lactate could positively amplify this angiogenic program, a process that requires a semicoordinated effort among multiple cells. Indeed, acidosis often precedes angiogenesis, and lactate may stimulate HIF expression independently of hypoxia (Fukumura et al., 2001; Lu et al., 2002; Shi et al., 2001). Cancer cells, by participating in a kind of quorum sensing and coordinating their metabolism, may therefore act as a pseudo-organ.

Metabolism as an Upstream Modulator of Signaling Pathways

Not only is metabolism downstream of oncogenic pathways, but an altered upstream metabolism may affect the activity of signaling pathways that normally sense the state of the cell. Individuals with inherited mutations in succinate dehydrogenase and fumarate hydratase develop highly angiogenic tumors, not unlike those exhibiting loss of the VHL tumor suppressor protein that acts upstream of HIF (reviewed in Kaelin and Ratcliffe, 2008). The mechanism of tumorigenesis in these cancer syndromes is still contentious. However, it has been proposed that loss of succinate dehydrogenase and fumarate hydratase causes an accumulation of succinate or fumarate, respectively, leading to inhibition of the prolyl hydroxylases that mark HIF for VHL-mediated degradation (Isaacs et al., 2005; Pollard et al., 2005; Selak et al., 2005). In this rare case, succinate dehydrogenase and fumarate hydratase are acting as bona fide tumor suppressors.

Mutations in metabolic genes, however, need not be a cancer-causing event. More subtly, the activation of various metabolic pathways might modulate the activity of downstream pro-cancer factors. Whereas it is well-accepted that growth factor signaling is commonly dysregulated in cancer, the involvement of nutrient or energy signaling in cancer remains unclear. In prokaryotes, various metabolites are sensed directly by the signaling machinery. The mammalian pathways that respond to energy and nutrient status may also interface with metabolites directly. It is well established that AMP-kinase senses the AMP/ATP ratio (reviewed in Hardie, 2007), whereas mTOR (the mammalian target of rapamycin) senses cellular amino acid concentrations (Kim et al., 2008; Sancak et al., 2008). Both AMP-kinase and mTOR have been linked to tumor syndromes. It is possible that one way to upregulate these pro-growth signaling pathways is to increase the levels of the normal metabolites that they sense.

Metabolism Upregulation Generates Toxic Byproducts

Although altered metabolism confers several advantages on the cancer cell, it does not come without disadvantages. As a consequence of a deranged or simply overactive metabolism, cancer cells may be burdened with toxic byproducts that require disposal. So far, there is relatively little evidence for this hypothesis in the existing literature, but a few examples do suggest that cancer cells require detoxification mechanisms to maintain survival. Although there are enzymes that detoxify exogenous toxins, several "house-cleaning" enzymes, a term coined from studies in bacteria, deal with endogenous toxic metabolites (reviewed in Galperin et al., 2006). The best example of "house-cleaning" enzymes are the NUDIX (noncanonical nucleoside diphosphate linked to some other moiety X) hydrolases, a family of enzymes that act on the nucleotide pool and remove noncanonical nucleoside triphosphates. When incorporated into the DNA, these aberrant nucleotides can lead to mismatches, mutations, and eventually cell death. The dUTP pyrophosphatase (DUT), which hydrolyzes dUTP to dUMP and prevents the incorporation of uracils into DNA, may play a role in resistance to thymidylate synthase inhibitors. Suppression of DUT sensitizes some cancer cells to pyrimidine antimetabolites, suggesting that inhibition of these cellular house-cleaning enzymes may be an effective adjunct chemotherapeutic strategy (Koehler and Ladner, 2004).

The lactate production associated with the shift to a glycolytic metabolism is thought to contribute to the acidification of the microenvironment. Able to adapt to and even benefit from an acidic environment, cancer cells have been shown to upregulate vacuolar H^+-ATPases, Na^+-H^+ antiporters, and H^+-linked monocarboxylate transporters (reviewed in Gatenby and Gillies, 2004). Inhibition of these adaptive mechanisms can lead to decreased viability of cancer cells and increased sensitivity to chemotherapeutic agents (reviewed in Fais et al., 2007; Fang et al., 2006).

Uncharted Territory

Many mysteries remain unsolved in our understanding of even normal human metabolism, let alone that of cancer cells. The metabolic pathways of the mammalian cell and their many interconnections are incomplete, as many enzymes remain unannotated in the human genome. Although we have guesses by homology, the identities of the human enzymes that catalyze reactions we know must occur are still elusive. In addition to annotating all human metabolic genes, the "ins" and the "outs" (i.e., the metabolites that enter and exit cells) should be measured and cataloged. It is also entirely unclear what percentage of the cellular fuel is normally used for ATP generation, biosynthesis, or other processes. And with few exceptions surprisingly little is known about intercellular metabolism. Much of our understanding of metabolism has been inherited from work in simple organisms; the compartmental nature of human metabolism is an exciting area of potential exploration.

Although aerobic glycolysis is the most characterized, although still puzzling, metabolic phenomenon in cancer, many other aspects of cancer metabolism are likely to be derangements of normal metabolism and ought to be elucidated. The nutrient conditions of the tumor microenvironment have not yet been carefully examined. Cancer cells, despite engaging in energy-costly processes, must still be able to maintain ATP levels, by either relying on increased flux

through glycolysis or utilizing a diversity of fuel sources. Several hypotheses exist as to why a fraction of tumors are refractory to imaging by FDG-PET. One possibility is that certain cancer cells may not be primarily glucose-metabolizers but may rely on alternative fuel sources, the detailed characterization of which may lead to the detection and treatment of "PET-negative" tumors. Furthermore, there are more complex questions to be answered: Is it possible that cancer cells exhibit "metabolite addiction"? Are there unique cancer-specific metabolic pathways, or combinations of pathways, utilized by the cancer cell but not by normal cells? Are different stages of metabolic adaptations required for the cancer cell to progress from the primary tumor stage to invasion to metastasis? How malleable is cancer metabolism?

From a therapeutic perspective, knowledge of the causes, benefits, and vulnerabilities of cancer cell metabolism will enable the identification of new drug targets and will facilitate the design of metabolite mimetics that are uniquely taken up by cancer cells or converted into the active form by enzymes upregulated in tumors. Profiling of either metabolites or enzymatic activities may allow us to develop diagnostic tests of cancer, and metabolite derivatives can be used for the molecular imaging of cancer, as exemplified by FDG-PET. We find the possibility of a new class of cancer therapeutics and diagnostic tools especially exciting. Therefore, we emphasize the need to explore beyond a glucose and energy-centric driven model of cancer metabolism to a broader one that encompasses all of the metabolic needs of a cancer cell. Perhaps it is time to step out from under Warburg's shadow.

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