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# Metabolic Targeting as an Anticancer Strategy: Dawn of a New Era?

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Current targeted therapeutics directed against cancer mainly involve specifically blocking molecular signals that promote tumor cell proliferation, obstruct cell death, hamper cellular differentiation, or facilitate angiogenesis. However, the molecular pathways that underlie these cellular processes are multifaceted and often redundant. An alternative approach may be to target tumor metabolism. Glycolysis “lyses” glucose, eventually yielding pyruvate, which is reduced to lactate, a process that does not require oxygen. In the presence of oxygen, pyruvate enters the tricarboxylic acid (TCA) cycle in mitochondria, leading to the production of adenosine triphosphate (ATP) through oxidative phosphorylation and also to the production of reactive oxygen species (ROS).

In the 1920s, Warburg noted that tumors exhibit increased rates of glycolysis even in the presence of oxygen, a phenomenon known as aerobic glycolysis or the “Warburg effect” (1). The Warburg effect is now considered a common property of cancer metabolism. The shift from oxidative phosphorylation to glycolysis that occurs in cancer cells in response to hypoxia and oncogenic changes is known as metabolic “remodeling” or adaptation (2). Because cancer cells have very high energy demands and glycolysis is far less efficient than oxidation in producing ATP (2 versus 36 ATP per glucose molecule, respectively), cancer cells must accelerate their rate of glucose uptake and usage. Indeed, this increase in glucose metabolism is the basis for positron emission tomography with <sup>18</sup>fluorodeoxyglucose (FDG-PET), an imaging technique used to detect cancer (3–5). Because of their constitutively up-regulated glycolysis, cancer cells generate large amounts of lactate that, for reasons not fully understood, are required for tumor maintenance, confer a growth advantage, and promote metastasis (2, 6).

The Warburg effect in cancer cells is likely caused by both genetic and epigenetic changes, although the precise molecular mechanisms remain poorly understood and controversial (2, 7). Defects in mitochondrial respiration and oxidative phosphorylation, a hypoxic microenvironment due to insufficient oxygen penetration in tumors, an increase in the expression (and thus activity) of glycolytic enzymes, and oncogene signaling may all contribute to the effect (7).

Metabolic adaptation in cancer cells may be an intrinsic part of carcinogenesis. Recent reports by Matoba *et al.* (8) and Bensaad *et al.* (9) provide a mechanism whereby mutation of p53 may promote a glycolytic metabolism. Matoba *et al.* demonstrated that p53 directly regulates oxidative phosphorylation by

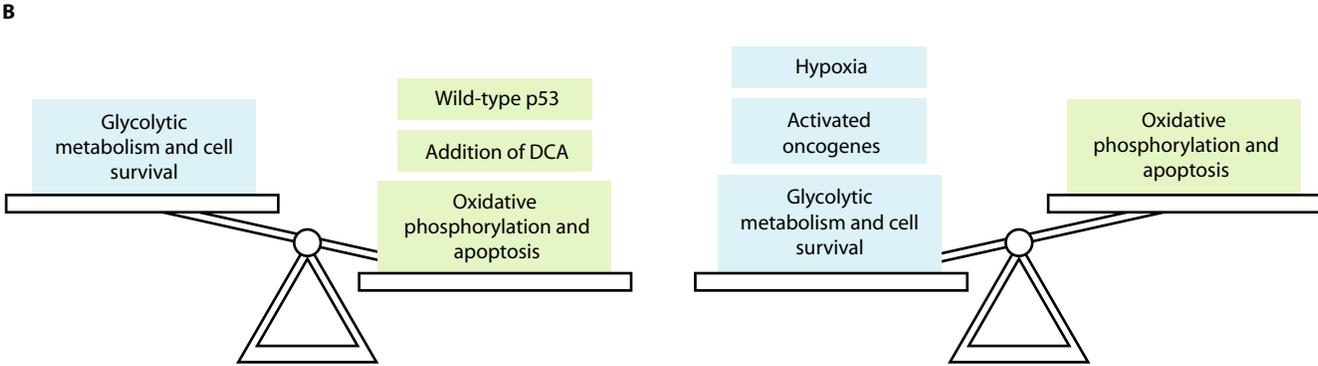
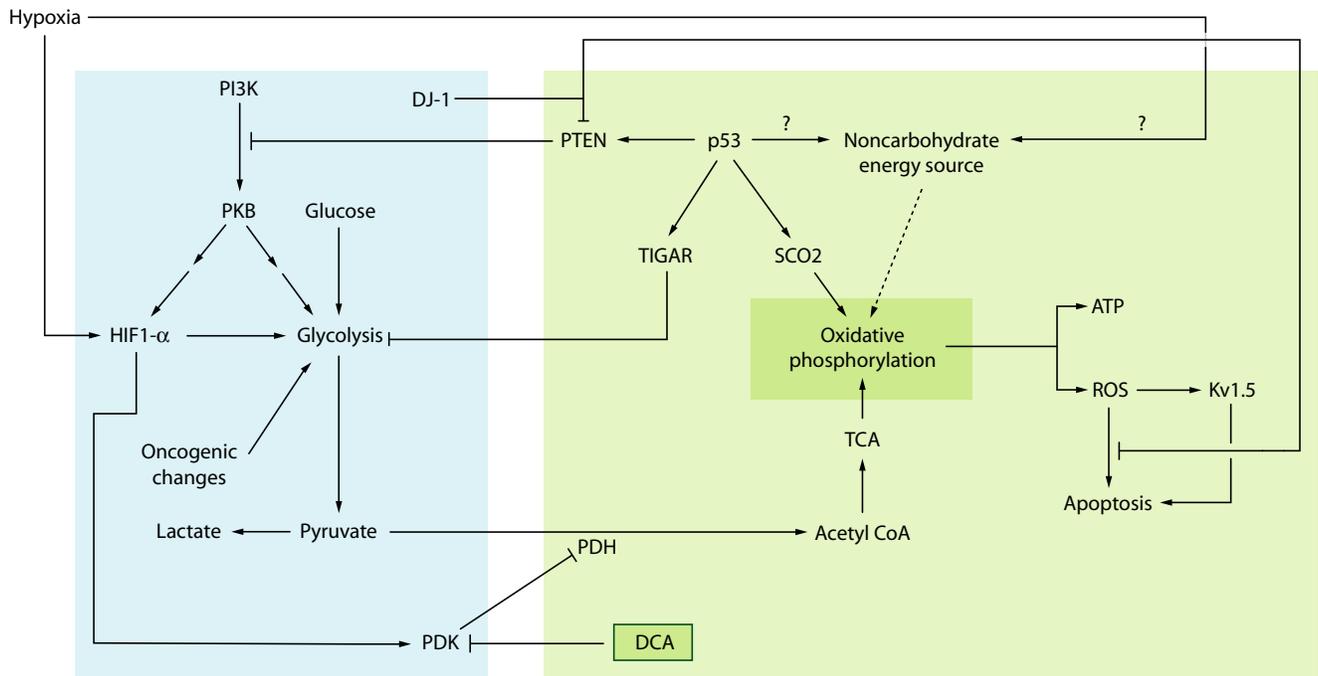
stimulating the expression of the gene encoding SCO2 (synthesis of cytochrome c oxidase 2). SCO2 is critical for the assembly of the cytochrome c oxidase (COX) complex embedded in the inner mitochondrial membrane, the major site of oxygen use in mammalian cells. Disruption of the *SCO2* gene in cancer cells bearing wild-type p53 produced a similar glycolytic metabolism as that observed in p53-deficient tumor cells. Bensaad *et al.* identified a p53-inducible gene named *TIGAR* (TP53-induced glycolysis and apoptosis regulator), which encodes a product that decreases fructose-2,6-bisphosphate (Fru-2,6-P<sub>2</sub>) concentration. Fru-2,6-P<sub>2</sub> is a potent positive allosteric effector of 6-phosphofructose-1-kinase (PFK-1), which promotes glycolysis. As a result, *TIGAR* expression attenuates glycolysis (9). Thus, p53, encoded by the gene most often mutated in cancer, affects the pathway of ATP generation in noncancerous cells by stimulating oxidative phosphorylation (through activation of SCO2) and inhibiting glycolysis (through inactivation of PFK-1) (Fig. 1). These findings imply that human cancers harboring p53 mutations may be susceptible to antimetabolic drugs designed to block glycolysis, because these tumors likely depend on glycolysis for growth and survival.

Hypoxia, which plays a key role in metabolic adaptation, is widely observed in tumors. Hypoxia promotes glycolysis and suppresses oxidative phosphorylation (2); both of these effects are attributable to the hypoxia-dependent increase in the abundance and activity of the transcription factor hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ). HIF-1 $\alpha$  induces the expression of genes that encode glucose transporters and glycolytic enzymes (10) and suppresses both the TCA cycle and oxidative phosphorylation. The latter effects are due to direct transactivation of the gene encoding mitochondrial pyruvate dehydrogenase kinase (PDK), a negative regulator of pyruvate dehydrogenase (PDH), the enzyme that catalyzes the conversion of pyruvate to acetyl-CoA before its entry into the TCA cycle (11, 12). Furthermore, HIF-1 $\alpha$ -mediated induction of PDK increases ATP production through glycolysis and, by further reducing oxidative phosphorylation and the associated production of ROS, protects cells from ROS-induced damage and death (Fig. 1). ROS-induced death of tumor cells is also inhibited by the putative oncogene DJ-1. DJ-1 inhibits the tumor suppressor PTEN (phosphatase and tensin homolog deleted from chromosome 10) and thereby activates the survival enzyme protein kinase B (PKB, also known as Akt), an effect that may allow DJ-1 to promote glycolysis (13–15) (Fig. 1). Like HIF-1 $\alpha$ , DJ-1 is up-regulated in many cancers. The expression of DJ-1 and other hypoxia-induced genes are associated with poor clinical outcomes (13, 16, 17).

An intriguing and provocative report by Bonnet *et al.* (18) suggests that the metabolic adaptation that occurs in tumor cells can be exploited to kill them. Dichloroacetate (DCA), a drug used to treat human lactic acidosis, inhibits PDK (19). Bonnet *et al.* discovered that DCA also selectively kills cancer cells by “normalizing” cancer-associated metabolic properties. DCA

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**Fig. 1.** The metabolism of glucose and its regulation by oncogenic signals. **(A)** Glycolysis breaks down glucose in the cytoplasm to generate pyruvate. In the absence of oxygen, pyruvate is reduced to lactate. In the presence of oxygen, pyruvate is oxidized by PDH to acetyl-CoA, which enters the mitochondria and the TCA cycle. Oxidative phosphorylation generates ATP as an energy source and also produces ROS. ROS can cause mitochondrial damage and apoptosis, both by stimulating the release of apoptotic factors and through activation of Kv1.5 channels. Glycolytic metabolism can be promoted by oncogenic changes. For instance, the tumor suppressor p53 inhibits glycolysis through *TIGAR* induction and stimulates oxidative phosphorylation through *SCO2* induction. In cancer cells with mutated p53, ROS-induced apoptosis is thus decreased. The oncogene DJ-1 also blocks ROS-induced apoptosis and may increase glycolysis by inhibiting PTEN and thereby activating PI-3' kinase and PKB. Hypoxia can induce glycolysis in cancer cells through HIF-1 $\alpha$  stabilization and activation, and thereby the up-regulation of glycolytic enzymes. Furthermore, hypoxia suppresses oxidative phosphorylation through the transcriptional activation of the gene encoding PDK. By inhibiting PDK, DCA may shift cancer cell metabolism back toward oxidative phosphorylation. Some cancer cells may use nonglucose energy sources such as amino acids, fatty acids, or nucleic acids. How p53 and hypoxia influence the metabolism of these energy sources is unknown. **(B)** Wild-type p53 and DCA shift cancer cells toward oxidative phosphorylation and apoptosis. Oncogenic changes and hypoxia shift cancer cells toward glycolytic metabolism and survival.

treatment suppressed glycolysis and promoted oxidative phosphorylation, thereby increasing mitochondrial H<sub>2</sub>O<sub>2</sub> (a relatively stable ROS). As a result, voltage-gated potassium channels (Kv) were activated (Fig. 1) (20).

The mitochondria-ROS-Kv axis is known to be involved in O<sub>2</sub> sensing as well as in the promotion of apoptosis, and down-

regulated Kv channel activity occurs in cancer cells of various tissue origins (21). Kv channels are redox-sensitive and activated by mitochondria-derived H<sub>2</sub>O<sub>2</sub>, a by-product of aerobic respiration (20). The inhibition or down-regulation of Kv channels suppresses apoptosis in multiple cell types, including tumor cells (22–24). Bonnet *et al.* confirmed previous work (25)

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showing that DCA inhibits PDK and thus activates Kv1.5 channels (18). More important, Bonnet *et al.* demonstrated that DCA-mediated inhibition of PDK in cancer cells led to depolarization of the mitochondrial membrane and subsequently to cell death by apoptosis. Overall tumor growth was thus suppressed. DCA treatment did not affect normal cells, which presumably had not undergone metabolic adaptation.

Bonnet *et al.* also showed that the selective killing of cancer cells by DCA occurs through two mechanisms: (i) DCA shifts cancer cell metabolism toward aerobic respiration such that depolarization of the mitochondrial membrane induces the release of proapoptotic factors from the mitochondria; and (ii) DCA promotes increased H<sub>2</sub>O<sub>2</sub> generation in cancer cells, which activates Kv channels (specifically, Kv1.5). Kv1.5 in turn inhibits the Ca<sup>2+</sup>-dependent transcription factor NFAT (nuclear factor of activated T lymphocytes), which is known to impair both apoptosis and the expression of Kv1.5 in myocardial cells (26, 27). DCA-mediated activation or up-regulation of Kv1.5 channels likely decreases cellular [K<sup>+</sup>]<sub>i</sub>, thus activating caspases and triggering the demise of the cancer cells (21–23).

Intriguingly, Bonnet *et al.* also used a rat implantation model of lung cancer to show that DCA has a therapeutic effect on established cancers. However, because the clinical use of DCA has been associated with peripheral nerve toxicity (28, 29), the clinical efficacy and toxicity profile of DCA as an anticancer agent will have to be carefully examined in clinical trials. If this toxicity can be tolerated and its efficacy demonstrated, DCA treatment may be an important example of anticancer intervention through metabolic targeting.

Although the above observations offer hope for a relatively simple and cost-effective way of specifically killing cancer cells by targeting their metabolism, the situation is likely to be more complicated in practice. Although glucose appears to be the major energy source fueling tumor cell survival and growth, and glycolysis is constitutively up-regulated in many cancer cells, it is also possible that these cells can use alternative energy sources and that nonglycolytic pathways are operational in cancers even under hypoxic conditions. For example, fatty acid (FA) oxidation may be a dominant bioenergetic pathway in prostate cancer cells (30). Fatty acid synthase (FAS), a key enzyme in FA metabolism, is up-regulated in many cancers (3–33), and FAS inhibitors have antitumor activity (33, 34). In addition, not all cancers are easily detected by FDG-PET (5, 30), which suggests that these malignancies either have a low rate of glycolysis or depend on a nonglucose energy source (Fig. 1). Drug- and radiation-resistant cancer cells use FA to support mitochondrial oxygen consumption when glucose becomes limited (35).

These lines of evidence indicate that tumor cell metabolism has intrinsic plasticity. Indeed, it has been documented that cancer cells can switch metabolic pathways or energy sources in response to nutrient depletion or fuel source limitation (36). Thus, the targeting of a single metabolic pathway, such as inhibiting glycolysis, may not be sufficient to eliminate tumor cells. Given the heterogeneity of human tumors and the instability of cancer cell genomes, a major challenge to the metabolic targeting strategy may be potential resistance to a single antimetabolic drug. Combination therapies that block multiple metabolic pathways should therefore be considered in both preclinical “proof of principle” trials and in clinical settings.

A picture is emerging whereby flexibility in tumor cell

metabolism allows cancers to adapt and thrive in environments in which glucose or oxygen or both may be limiting. Understanding the energy sources and metabolic pathways used by cancer cells under these circumstances should allow the exploitation of these new principles for cancer treatment.

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