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Carbon Source Metabolism and Its Regulation in Cancer Cells

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Abstract

Cancer cell proliferation and progression require sufficient supplies of nutrients including carbon sources, nitrogen sources, and molecular oxygen. Particularly, carbon sources and molecular oxygen are critical for the generation of ATP and building blocks, and for the maintenance of intracellular redox status. However, solid tumors frequently outgrow the blood supply, resulting in nutrient insufficiency. Accordingly, cancer cell metabolism shows aberrant biochemical features that are consequences of oncogenic signaling and adaptation. Those adaptive metabolism features, including the Warburg effect and addiction to glutamine, may form the biochemical basis for resistance to chemotherapy and radiation. A better understanding of the regulatory mechanisms that link the signaling pathways to adaptive metabolic reprogramming may identify novel biomarkers for drug development. In this review we focus on the regulation of carbon source utilization at a cellular level, emphasizing its relevance to proliferative biosynthesis in cancer cells. We summarize the essential needs of proliferating cells and the metabolic features of glucose, lipids, and glutamine, and we review the roles of transcription regulators (i.e.,HIF-l, c-Myc, and p53) and two major oncogenic signaling pathways (i.e., PI3K-Akt and MAPK) in regulating the utilization of carbon sources. Finally, the effects of glucose on cell proliferation and perspective from both biochemical and cellular angles are discussed.

Keywords

c-Myc; glutaminolysis; HIF-1; MAPK; metabolism; PI3K; Warburg effect

I. INTRODUCTION

Normal cell physiology requires a sufficient supply of reduced carbon sources for the generation of ATP, building blocks and reducing power. The rapid proliferation of tumor cells increases these fundamental needs, which in turn demands accelerated utilization of carbon sources. However, solid tumors frequently outgrow their blood supply, which leads to insufficient carbon sources, nitrogen sources and molecular oxygen. One well-known adaptive strategy is angiogenesis, and the heterogeneous nature of tumor-associated

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angiogenesis leads to uneven distribution of blood flow, resulting in ischemic lesions in solid tumors. Therefore, cellular level metabolic adaptation to nutrient insufficiency is critical for tumor progression and invasion. Two prominent characteristics of tumor cell metabolism are the Warburg effect and glutaminolysis, which respectively illustrate the dependence of tumor cells on glucose and glutamine.

Distinguishable from the Pasteur effect, which reflects anaerobic fermentation of glucose, the Warburg effect is defined as the increased glucose consumption and lactate secretion in tumor cells even in the presence of sufficient oxygen.[1] Based on experimental data, Warburg proposed that in cancer cells the glucose utilization was switched from oxidative phosphorylation to glycolysis.[1] The Warburg effect successfully drew the attention of cancer biologists to the glucose metabolism in cancer cells. As increased glucose uptake was observed in various cancer cell lines with the application of the imaging technique ^{18} fluorodeoxyglucose (FdG) positron-emission tomography (PET), the Warburg effect has been recognized as a universal metabolic feature of a variety of cancers.[2, 3]

Glutamine has been considered as an important nutrient for cultured cells since the 1950s. Enhanced glutaminolysis has been observed in various types of tumors. It is generally believed that through glutaminolysis, glutamine provides another type of reduced carbon source, which facilitates the biosynthesis of macromolecules, energy production, and redox maintenance.[4–8]

Here, we review carbon source metabolism in cancer cells, focusing on recent literature that has advanced our understanding of how different types of carbon sources satisfy the needs of cancer cell survival, growth, and proliferation. We summarize how oncogenic pathways regulate carbon source utilization by reprogramming the gene transcription or by altering the activity of metabolic enzymes, and we discuss how cancer cells sense and respond to changes of glucose availability.

II. TYPES OF CARBON SOURCES AND PHYSIOLOGICAL ROLES

Three types of organic molecules are utilized by human cells as carbon sources: carbohydrates, amino acids, and lipids. Cell proliferation dictates the generation of ATP and organic molecules of cell components as well as the reducing power in the form of NADPH from the carbon sources. Although the utilization of carbon sources by cells *in vivo* is a rather complicated issue, the establishment of cell culture models has simplified the analysis of nutrient needs to support cell survival and proliferation. Fatty acids can be used directly for the biosynthesis of phospholipids or for the production of acetyl-CoA, which can be used for ATP production or biosynthesis. It is generally accepted that all cells can synthesize fatty acids to meet the needs of biomembrane biosynthesis during cell proliferation, and acetyl-coA can be obtained from carbohydrates and amino acids. Therefore, it is not surprising to note that fatty acids are not needed in cell culture media. In optimized cell culture media, in addition to essential nutrients, abundant amounts of glucose and glutamine are added. Notably, while animal sera are added generally to meet the needs of growth hormones, they also contain glucose, glutamine, fatty acids and other nutrients. When dialyzed sera are used in studies, it has been shown that both glucose and glutamine are absolutely required for

most cell types,[9] suggesting that each has an indispensible role in supporting cell proliferation. Therefore, glucose and glutamine, two non-essential nutrients at the organismal level, are essential for most cells cultured *ex vivo*.

A quick review of the biochemical and metabolic features of different types of carbon sources may help our understanding of their importance and their unique roles in cancer cell metabolism (Figure 1). To facilitate the discussion, we have listed the major enzymes (including transporters) implicated in the utilization of glucose and glutamine as carbon sources in Table 1. Upon entering cells, the majority of glucose is phosphorylated to form glucose-6-phosphate (G6P), which is the substrate for multiple metabolic pathways, including the glycolytic and pentose phosphate pathways. Through sequential glycolysis and pyruvate dehydrogenation, glucose provides acetyl-CoA, which can be used either for biosynthesis or for ATP production through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. Even under hypoxic conditions, glucose can support ATP production through fermentation. Through the pentose pathway, glucose satisfies the needs of NADPH. ATP, acetyl-CoA, NADPH and other intermediate metabolites of glycolysis, the pentose phosphate pathway, and the TCA cycle satisfy the needs for biosynthesis of a variety of biomolecules, including non-essential amino acids, fatty acids, and nucleotides. On the other hand, the use of fatty acids is limited to being oxidized to acetyl-CoA, which can be used to generate ATP or can participate in biosynthesis. Therefore, metabolically, glucose is a versatile reduced carbon source that should be sufficient to meet all cellular needs for carbon. In addition to carbohydrates and lipids, amino acids represent another type of carbon source. Particularly, glutamine provides carbon through glutaminolysis and subsequent conversion of glutamate to α-ketoglutarate. Given the roles of glutamine and glutamate in nitrogen anabolism, it is not difficult to appreciate their essentiality in cell culture systems.[9] Then why cannot glutamate, which is eventually catabolized to α-ketoglutarate, be directly used in cell culture to replace glutamine? One obvious explanation could be that cells do not have effective transporters to uptake sufficient amounts of glutamate. In fact, cells need to maintain high levels of glutamate intracellularly. In addition to serving as a central hub to balance the amino acid pool through various transamination reactions, glutamate is required for multiple biosynthetic pathways that need nitrogen. Biosynthesis of glutathione and polyamines are two rather important examples. Upon entering the TCA cycle, the glutamine-derived α-ketoglutarate may end up in numerous organic metabolites; some may serve as a substrate for the production of NADPH.[10] However, in the presence of glucose and pentose pathway, this function does not justify its essentiality for cell proliferation. Theoretically, α-ketoglutarate from glutaminolysis may be used in gluconeogenesis, or it may be converted to other organic molecules through anaplerotic pathways. In most cases, however, glutamine cannot support cell proliferation in glucose-free media, suggesting that the carbons from glutamine catabolism are not capable of completely replacing glucose. Moreover, replenishing intracellular α-ketoglutarate or oxaloacetate levels cannot rescue cell growth in glutamine-free media, either.[9] If alternative pathways to generate glutamate in cells are provided, cells become capable of growing in glutamine-free media, indicating that the carbons from glutamine catabolism are not absolutely necessary for cell proliferation. Therefore, although glutaminolysis provides an

alternative source of carbon, its essential role in supporting cell proliferation may be as a precursor of glutamate and, as such, participates in various nitrogen anabolic pathways.

III. HOMEOSTATIC REGULATION OF CARBON SOURCE UTILIZATION

It is generally accepted that tumor cells require an increased, undisrupted supply of energy to support their survival, growth, and proliferation. Like normal cells, tumor cells continuously monitor the intracellular ATP levels, and accordingly they regulate the oxidation of the carbon source. The bioenergetic processes are homeostatically regulated by changes of ATP and ADP levels, which have been detailed in most biochemistry textbooks. In eukaryotic cells, the concentrations of ATP and ADP are much higher than that of AMP; a slight decrease of ATP level leads to a remarkable change of AMP levels. Therefore, change of AMP concentration is a more sensitive indicator of energy status. Accordingly, the AMP-activated protein kinase (AMPK) pathway has a very crucial role in the process. When the cellular ATP level is low, AMP concentration increases, which allosterically activates AMPK. Increased AMP levels also protect phosphorylated AMPK from dephosphorylation.[11–15] Activated AMPK enhances ATP levels by coordinately reprogramming several cellular processes. First, AMPK inhibits the biosynthesis of fatty acids, cholesterol, glycogen, and proteins, conserving energy and diverting more carbon sources to ATP production.[16–19] Second, AMPK activation stimulates catabolic pathways to increase ATP production; AMPK activates many catabolic enzymes participating in the glycolysis and fatty acid oxidation.[20, 21] Third, AMPK activation can also cause a Gl phase cell cycle arrest and prevent the entry into S phase where a large amount of ATP is required.[22] In normal myocytes and adipocytes, AMPK has been reported to collaborate with the insulin signaling pathway to promote the translocation of glucose transporter 4 (GLUT 4)[23] and in the long term the expression of GLUT4.[24] By increasing the transcriptional coactivator PGC-lα, AMPK can up-regulate mitochondrial biogenesis as well,[25] facilitating ATP production and cellular adaptation. By enhancing ATP production and inhibiting ATP consumption, the AMPK pathway delicately maintains the energy homeostasis in tumor cells.

For all types of cells, a balance between reducing power and oxidizing power is crucial for normal cell function. In most cases, molecular oxygen serves as the final electron acceptor, being the major oxidizing power in cells. Two important molecules working as the reducing power are NADPH and glutathione (GSH). By donating electrons to oxidized glutathione (glutathione disulfide, GSSG), NADPH maintains the homeostatic ratio of [GSH]/[GSSG]. NADPH and GSH collaboratively protect enzymes and cellular structures from damage by free radicals or non-radical reactive oxygen species (ROSs). Although ionization and UV are considered the exogenous sources of free radicals or ROSs, incomplete reduction of oxygen during oxidative phophorylation in mitochondria serves as the major endogenous source of ROSs. In addition, oxidations catalyzed by other oxidoreductases such as NAD(P)H oxidases and xanthine oxidase may generate ROSs as well.[26] Whereas adequate levels of ROS have various biological functions, ranging from signal transduction to regulation of gene expression,[27] high levels of ROSs can cause damage to macromolecules, including DNA, proteins, and lipids.[28] Recently it has been reported that ROSs also activate protein kinase C delta (PKC delta) to stimulate senescence[29] and trigger the release of cytochrome c

by permeating the mitochondria,[30, 31] which eventually leads to apoptosis. Finally, the role of NADPH in reductive biosyn-thetic reactions as electron donor has been well established.

The ratio of [NADPH]/[NADP+] is dynamically maintained by oxidizing reduced carbon sources. Metabolically, NADP+ can be converted to NADPH in several ways: (1) the pentose phosphate pathway, which oxidizes phosphorylated glucose, G6P; (2) the reaction catalyzed by malic enzyme 1 (ME1) with malic acid as the substrate;[10] and (3) the oxidation of glutamate catalyzed by glutamate dehydrogenase; and (4) the reaction converting isocitrate to α-ketoglutarate catalyzed by isocitrate dehydrogenase 1 and 2 (IDH 1 and 2) in cytosol, which has been recently discovered to use NADP+ as a cofactor, generating NADPH.[32] It is generally accepted that the pentose pathway, which directly uses G6P as substrate, is a universal and the most important mechanism. Accordingly, this pathway is homeostatically regulated by the cytosolic NADPH levels. The rate-limiting enzyme of the pentose phosphate pathway (PPP) is glucose-6-phosphate dehydrogenase (G6PD), which catalyzes the first of the two oxidation steps of the PPP. An increase of NADPH allosterically represses G6PD activity, serving as a negative feedback mechanism.

Another major need of carbon sources is the biosynthesis and maintenance of biomembranes, which require the synthesis of phospholipids and sterols. The biosynthesis of phospholipids requires the synthesis of fatty acids, cholesterol, and glycerate-3-phosphate. The regulation of fatty acid and cholesterol biosynthesis has been extensively studied, mostly in hepatocytes and adipocytes in the context of adipogenesis. The *de novo* synthesis of sterols is controlled by sterol regulatory element (SRE) and SRE-binding proteins (SREBPs). SREBPs are a family of membrane-bound transcription factors. Normally SREBPs are inserted in the membranes of endoplasmic reticulum (ER), bound to the SREBP cleavage-activating protein (SCAP), which is both the escort of SREBP and the sterol sensor. When the intracellular sterol level is low, SREBP migrates to the Golgi apparatus, where SREBP is cleaved by site-1 and site-2 proteases (S1P and S2P) which are activated by SCAP. The cleaved SREBP then moves into the nucleus and acts as a transcription factor to up-regulate the transcription of more than 30 genes; most of which are involved in the synthesis or uptake of cholesterol, fatty acids, phospholipids, and triacylglycerols.[33] The nuclear hormone receptors liver X receptors (LXRα and LXRβ interact with retinoid X factor (RXR) and function as heterodimeric transcription factors.[34] In response to an increase of cholesterol and particularly oxysterols, LXR/RXR dimers bind to LXR-responsive elements (LXRE, AGGTCAnnnnAGGTCA) and up-regulate the expression of SREBP-lc, ChREBP, and genes involved in adipogenesis.[35] Finally, the peroxisomal proliferator-activated receptors (PPARα , -β, -γ) are also known for regulating the utilization of glucose and lipids.[36] However, it remains unclear whether these regulatory mechanisms for lipogenesis are fully or partly adopted for the production of biomembranes during cell division. How tumor cells sense the levels of fatty acids and glycerate-3-phosphate during cell proliferation also remains an interesting question.

Finally, several non-essential amino acids, including glutamine, glutamate, aspartate, serine, and glycine, are needed in large quantities in actively proliferating cells. These amino acids are either abundant in proteins or are required for the biosynthesis of nucleotides, heme, and other nitrogenous molecules. Glutamine fulfills cancer cells' needs for glutamine and

glutamate. Biosynthesis of alanine, aspartate, serine, and glycine make demands on the supply of carbon skeletons in the form of intermediate metabolites such as pyruvate, oxaloacetate, and 3-P-glycerate. Major enzymes required for the synthesis of these important metabolites are provided in Table 1 as well.

IV. TRANSCRIPTIONAL REGULATORS OF CARBON SOURCE METABOLISM IN TUMOR CELLS

Because cancer cell proliferation demands the synthesis of DNA, RNA, proteins, and biomembranes, oncogenic transformation should be able to promote the utilization of reduced carbon sources. Moreover, it is reasonable to argue that the oncogenic signaling pathways should coordinate the production of ATP, NADPH, acetyl-CoA and other organic metabolites that are needed in the biosynthesis of non-essential amino acids, nucleotides and phospholipids. Therefore, oncogenic transformation can be predicted to be associated with metabolic reprogramming, an essential process at least partly achieved by transcriptional reprogramming of genes involved in metabolism. Extensive studies have implicated many transcription factors in reprogramming gene expression in tumor cells.

HIF-1 is the major transcription factor regulating the expression of many genes in response to low oxygen conditions. HIF-1 is a heterodimer composed of the constitutively expressed HIF-1 β (also known as ARNT) and the function-determinant HIF-1 α. In the presence of oxygen, HIF-1 α is hydroxylated by oxygen-activated prolyl hydroxylase enzymes, then is recognized by tumor suppressor von Hippel-Lindau (VHL), an E3 ubiquitin ligase, and finally is degraded by the proteasome.[37] HIF-1 can up-regulate the transcription of many genes to promote glucose utilization (Table 2), such as glucose transporter 1 (GLTU1) and glycolytic enzymes including lactate dehydrogenase A (LDH A), which diverges pyruvate to lactate.[38–40] To promote cellular adaptation to the acidosis caused by increased fermentation, HIF-1 enhances the expression of the carbonic anhydrase CAIX and the lactate/H^+ symporter MCT4.[41, 42] In addition to promoting the glycolytic pathway, HIF-1 also activates the pyruvate dehydrogenase kinase (PDK1), which deactivate the mitochondria pyruvate dehydrogenase complex.[43] As such, HIF-1 activation represses the generation of acetyl-CoA from pyruvate, slows down the Krebs cycle, and indirectly inhibits oxidative phosphorylation.

The transcription factor c-Myc is responsible for many human cancers.[44] Genes up-regulated by c-Myc also contribute to promoting the glycolytic phenotype in tumor cells (Table 3). It has been established that the expression of many glycolytic enzymes such as GLUT1, hexokinase 2 (HK2), phosphofructokinase (PFKM), and enolase 1 are stimulated by c-Myc.[45–47] As HIF-1 also up-regulates these glycolytic enzymes, one can infer that c-Myc and HIF-1 are functionally related and interplay with each other to regulate glucose metabolism under various conditions. In addition to these enzymes, which are directly involved in glycolysis, c-Myc and HIF 1 also enhance the expression of lactate dehydrogenase (LDH), which facilitates the lactate formation and NAD+ regeneration. On the other hand, they inhibit mitochondrial oxidative phosphorylation by up-regulating pyruvate dehydrogenase kinase 1 (PDK1), which phosphorylates and inhibits pyruvate dehydrogenase (PDH), reducing the entry of pyruvate into the TCA cycle.[46]

As a tumor suppressor and a transcription regulator, p53 is well known for its role in growth arrest, DNA damage response and apoptosis.[48] Recent studies reveal that it is also an important regulator of cell metabolism.[49, 50] Active p53 contributes to promoting oxidative phosphorylation and to slowing down glycolysis. Wild-type p53 inhibits glucose uptake by reducing the expression of GLUT1 and GLUT4. It also has been reported that p53 increases the expression of cytochrome c oxidase 2 (SC02), an enzyme required for assembly of the mitochondrial electron transport chain.[51] As a target gene of p53, TP53-induced glycolysis and apoptosis regulator (TIGAR) decrease the level of fructose-2,6-biphosphate, which is an allosteric stimulator of phosphofructose kinase 1 (PFK1), the key regulatory enzyme of the glycolytic pathway.[52, 53] Considering the inhibitory effect of p53 on glucose utilization, and the high incidence of p53 mutation in many tumors, p53 mutation likely not only promotes the malignant transformation and tumorigenesis but also facilitates the altered carbon utilization in tumor cells.

Both p53 and c-Myc regulate the utilization of amino acids. As an oncogene, c-Myc has been shown to promote the catabolism of glutamine in tumor cells. At the beginning of glutamine-utilizing processes, glutamine transporters are required for glutamine uptake by tumor cells. Upon entering the cells, glutamine is first hydrolyzed by a procedure termed glutaminolysis that is catalyzed by glutaminases. It has been shown that knockdown of c-Myc significantly decreased the expression of high-affinity glutamine transporters ASCT 2 and SN2, suggesting that c-Myc has an essential role in glutamine uptake.[54] In addition, c-Myc has been also reported to activate glutaminolysis by repressing the expression of miR-23a/b, a microRNA that directly targets glutaminase 1 (GLS).[55] On the other hand, as a tumor suppressor, p53 up-regulates glutaminase 2 (GLS2).[56, 57] Whereas the biological significance of the differential regulation of glutaminase 1 and 2 remains elusive, up-regulation of glutaminase 1 is more closely related to tumor cell metabolism.

V. ONCOGENIC PATHWAYS PROMOTE THE UTILIZATION OF CARBON SOURCES IN TUMOR CELLS

Cell proliferation demands the coordinated production of energy, reductive equivalents, and building blocks.[58] This coordination is mainly controlled by transcriptional reprogramming that results from the activation or inactivation of specific transcription factors. Therefore, it is not surprising to realize that oncogenic signaling pathways can regulate transcription factors and can eventually facilitate the carbon source utilization, rendering distinct metabolic features of tumor cells, such as the Warburg effect and active glutaminolysis.[9] Among a variety of oncogenic signaling pathways, PI3K-AKT and MAPK represent the two most common ones activated in human tumors.

The PI3K-AKT signaling pathway is a critical cascade with various physiological functions, such as regulating cell survival, proliferation, motility, and promoting metabolism and angiogenesis.[59, 60] It has been well-established that under physiological conditions, insulin activates the PI3K-AKT pathway. In tumors, other stimuli may activate this pathway in an insulin-independent manner; constitutive activation of the PI3K-AKT pathway induces tumorigenesis.[61] Furthermore, maintaining the activation of PI3K-AKT pathway contributes to the coordination of tumor cell metabolism with rapid cell growth. The PI3K-AKT

pathway is activated by the binding of growth factors or insulin to receptor tyrosine kinases (RTKs).[59, 61] In addition to ligand binding, mutation of the tumor suppressor phosphatase and tensin homolog (PTEN) also leads to the activation of the PI3K-AKT pathway.[62]

AKT, also known as protein kinase B (PKB), has a central role in tumor cell metabolism. Activated AKT phosphorylates and inactivates TSC2, resulting in the activation of Rheb GTPase, which directly activates the mammalian target of the rapamycin complex 1 (mTORCl), an important factor in reprogramming the transcription and the metabolism of tumor cells.[63] Particularly, activated mTORCl leads to the accumulation of HIF-lα,[64] resulting in upregulation of HIF-responsive genes, such as GLUT1, HK2, and LDH.[65] Increased glucose uptake and HK2 activity facilitates tumor cells to trap glucose as glucose-6-phosphate, which is the substrate for multiple metabolic pathways, including glycolysis and the pentose phosphate pathway.[64] In addition, AKT enhances the transcription of phosphofructokinase-2 (PFK2)[66] and directly phosphorylates and activates PFK2.[67] A PFK2 product, fructose-2,6-bisphosphate, leads to allosteric activation of PFK1 that increases the glycolytic flow. The activation of the PI3K-AKT-mTORCl signaling pathway induces HIF-lα expression, which in turn enhances pyruvate kinase isoenzyme type M2 (PKM2) expression through collaboration with c-Myc-hnRNPs splicing regulators.[68] Increased PKM2, along with other glycolytic enzymes, enhances aerobic glycolysis.[68] Finally, activated AKT enhances the glucose uptake through upregulating the expression of GLUT1, GLUT2, and/or translocation of GLUT4 to the plasma membrane.[69, 70] AKT also coordinates the carbon source metabolism to facilitate lipid synthesis. The accumulation of HIF-lα by mTORCl leads to the up-regulation of ATP-citrate lyase (ACL), which cleaves citrate from the TCA cycle for acetyl-CoA generation in cytosol, which can be used for the synthesis of fatty acids and cholesterol.[11] Moreover, AKT may activate ACL by directly phosphorylating it.[71] PI3K-AKT-mTORCl has been shown to activate SREBP through enhancing its trafficking from the endoplasmic reticulum to the Golgi apparatus and to subsequently facilitate proteolytic processing to produce its active form.[72, 73] Additionally, PI3K-AKT has been reported to increase the expression of fatty acid synthase (FASN) to facilitate fatty acid synthesis in prostate cancer cell lines and primary tumors. [74, 75] The MAPK signaling pathway is critical in the regulation of cellular metabolism. It is activated by the sequential phosphorylation/activation of a cascade of kinases including MAPKKK, MAPKK, and MAPK.[76] Eventually, activated MAPK phosphorylates the targeted proteins to perform biological functions. Four mammalian MAPK signaling pathways have been reported: extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), p38, and ERK5.[77] MAPK has been reported to regulate a series of cellular processes, such as cell survival, differentiation, proliferation, motility, and stress responses.[78–80] In human MCF-7 breast cancer cells, the MAPK inhibitor PD98059 reduces insulin-induced glucose uptake and inhibits tumor cell proliferation.[81] In simulated T lymphocytes, ERK1/2 has been shown to induce glucose uptake and glycolysis by increasing the expression and activation of HK.[82] p44/p42 MAPK also regulates HIF transactivation through enhancing the formation of the HIF-p300/CBP complex.[83, 84] Moreover, ERK1/2 has been reported to phosphorylate TSC2, leading to the dissociation of the TSC1-TSC2 complex and the activation of the mTOR signaling pathway.[85] Activated mTOR phosphorylates S6K and 4E-BP1 that control translation.[59, 72] Due to mTOR's critical role in metabolism, it has been

suggested that MAPK may control tumor cell metabolism through activating mTOR. ERK1/2 also regulates the uptake and metabolism of glutamine in activated T lymphocytes.[86] ERK1/2 activation by CD28 induces the expression of the SNAT (SLC38) family of transporters that increase glutamine uptake.[86] Moreover, ERK1/2 coordinates glutamine uptake with glutamine metabolism through increasing the activity of glutaminase, glutamine dehydrogenase, glutamic-oxaloacetic transaminase, and glutamic-pyruvic transaminase.[86] Glutamine addiction and active glutaminolysis are metabolic characteristics of highly proliferating tumor cells.[9] The constitutive activation of MAPK in human tumor indicates that it may participate in glutamine metabolism. In addition, p38 MAPK, activated by MKK6/3, has been shown to promote glucose transport through enhancing the expression of GLUT, 1 regardless of the stimulus.[87] In addition to these factors, PI3K-AKT and ERK1/2 have been reported to up-regulate c-Myc expression in tumor cells,[88, 89] which controls the expression and activity of enzymes involved in glucose or glutamine metabolism. Accordingly, c-Myc also has been proposed to lead to Warburg effect or active glutaminolysis.[90–92]

VI. ADAPTIVE METABOLISM OF TUMOR CELLS TO GLUCOSE AVAILABILITY

Whereas oncogenic transformation may promote utilization of glucose by a tumor cell, glucose availability may alter the metabolism of tumor cells. Normal cells respond to glucose concentrations via modulating the glucose transporter activity, hexokinase activity, and the activities of other enzymes of carbon metabolic pathways, depending on the cell types. These responses are generally triggered either directly by extracellular glucose concentrations or indirectly by glucose homeostatic hormones including insulin, glucagon, and epinephrine. The tissue-specific expression of receptors of the hormones, glucose transporters, and isoenzymes forms the biological bases for tissue-specific responses of normal cells to glucose fluctuation. Hormone-mediated systematic responses have been studied extensively; an emerging concept is that physiological responses to glucose availability also occur at the cellular level. While the precise mechanism underlying the glucose sensing at a cellular level remains elusive, two transcription complexes have been found to regulate gene expression in response to high concentrations of glucose: MondoA:Mlx and MondoB:Mlx. The basic helix-loop-helix-leucine zipper (bHL-HZip) dimeric transcription factor MondoA:Mlx complex shuttles between the outer mitochondrial membrane (OMM) and the nucleus, depending on the intracellular glucose concentration.[93, 94] When the intracellular level of glucose increases, the MondoA:Mlx complex migrates into the nucleus and up-regulates its target genes, which are summarized in Table 4. MondoB is also called a carbohydrate response element binding protein (ChREBP); it was originally identified to physically interact with the carbohydrate response element (ChoRE). ChoRE was first found in a number of rodent genes involved in glycolysis and lipid metabolism, such as L-type pyruvate kinase (LPK) and acetyl-CoA carboxylase (ACC).[95–97] Based on these DNA motifs, ChREBP was identified.[98, 99] Elegant work from Ma et al. demonstrated that in response to high glucose, MondoB:Mlx plays a major role in stimulating glucose sensitive genes in liver.[100] Whereas MondoA and MondoB up-regulate an overlapping repertoire of genes in response to high glucose levels (Table 5),

their tissue-type-specific expressions are different. MondoA is highly expressed in skeletal muscle, whereas MondoB is highly expressed in the liver.[101, 102] Consistently, knockout of Mondo B impairs the lipogenesis in mouse liver.[103] Analysis of the functions of up-regulated genes revealed that the MondoA:Mlx and MondoB:Mlx-mediated transcriptional reprogramming leads to enhanced catabolism of glucose, enhanced utilization of glucose for carbon anabolism, but decreased glucose uptake. These responses clearly represent adaptive metabolic alterations.Transcriptional reprogramming to low glucose concentrations has not been extensively studied. As discussed, the AMP-activated protein kinase (AMPK) pathway serves as a prominent energy sensor. Any decrease in the ATP:AMP ratio upon glucose deprivation may trigger AMPK, which in turn inhibits biosynthesis activities. When glucose deprivation is continuous, AMPK can further work as an intrinsic regulator of the cell cycle that coordinates cellular proliferation with carbon source availability. In response to glucose deprivation, activated AMPK collaborates with cAMP-responsive element-binding protein (CREB) to transcriptionally regulate the expression of p53, a well-known inhibitory factor of cell proliferation.[22, 104, 105] AMPK can also inhibit the mTOR signaling pathway by phosphorylating the tuberous sclerosis complex protein 2 (TSC 2), the negative regulator of mTOR. The inactivation of the mTOR pathway can then contribute to protecting tumor cells from apoptosis under glucose-deprived conditions.[19] AMPK also protects tumor cells partially via induction of dual-specificity phosphatases (DUSPs), which suppress pro-apoptotic extracellular signal-regulated kinase (ERK).[106] In prostate cancer cells, glucose deprivation activates c-Jun N-terminal kinase (JNK), which can promote cell survival in the early phase and induces apoptosis in the late phase, and the AMPK signaling pathway works as the key regulator of the dual function of JNK.[107] In colorectal cancer cells, glucose deprivation induces the increased expression of receptors for adiponectin, which promotes cell survival through enhancing autophagy by activating AMPK and PPARα, but inhibiting PI3K-AKT pathway.[108] In addition to activating the AMPK signaling pathway, glucose deprivation also induces AMPK-independent responses. Several genes have been reported to be triggered by low glucose via AMPK-independent mechanisms. In MCF-7 cells, glucose deprivation is reported to reduce synthesis of collagen, the main component of extracellular matrix.[109] Follistatin, which is traditionally recognized as a secretory protein that inactivates extracellular activin, myostatin, and bone morphogenic proteins, has been reported to promote cancer cell survival under glucose-deprived conditions through inhibiting cellular rRNA synthesis.[110–113] Glucose deprivation also stimulates *O*-GlcNaA modification of proteins through up-regulation of *O*-Linked *N*-acetylglucosaminyltransferase, which may play a role in nutrition sensing.[114–116] At the protein level, glucose deprivation leads to Chkl degradation through the ubiquitin-proteasome pathway, which is a key regulator in the DNA replication checkpoint.[117]

VII. PERSPECTIVES AND CONCLUSION

Carbon source utilization is fundamental for cell proliferation and tumor growth. The Warburg effect is the most obvious biochemical feature of most tumor cells. Although it has been found for more than 80 years, its biological role in tumor progression remains elusive. Using glycolysis as the major way to produce ATP seems to be a disadvantage for tumor cells in competing with surrounding normal cells for carbon sources. One proposed

explanation is that metabolites produced in glycolysis facilitate rapid carbon anabolism, such as biosynthesis of non-essential amino acids and lipids, to satisfy the increased demand for growth and proliferation of tumor cells. Under anaerobic conditions, fermentation is required to regenerate oxidized NAD+ so fermentation can continue to provide ATP. Stoichiometrical analysis shows that all glyceraldehyde-3-phosphate molecules entering into the oxidative phase need to be eventually reduced to lactate to maintain the balance between NAD+ and NADH. Therefore, if the Warburg effect provides metabolites for biosynthesis, the metabolites are limited to those available prior to entering the oxidative stage of glycolysis. Another explanation suggests that increased generation of lactate results in acidosis in the tumor microenvironment, which is advantageous for tumor metastasis and invasion, and facilitates the removal of surrounding normal cells.[118] However, it is equally valid to consider the tumor metastasis and invasion as an adaptive consequence for tumor cells fighting the disadvantageous microenvironment of acidosis. Finally, lactate formation may be simply a consequence secondary to the inhibition of oxidative phosphorylation in tumor cells, representing an intriguing preference of tumor cells to use pyruvate instead of molecular oxygen as the oxidizing power. Further studies and systematic analyses of the carbon metabolic networks in tumor cells are required to understand the pathobiological significance of the Warburg effect in tumor cells.

Considering the complexity of carbon metabolic networks, both glucose and glutamine can be the ultimate substrates for NADPH production (Figure 1). However, when the glutamine carbon skeleton enters into the PPP, it requires an anaplerotic process followed by gluconeogenesis; its efficiency may be limited by cell-type-specific metabolic features. Generation of NADPH by ME1- or IDHl,2-catalyzed reactions requires the conversion of glutamine to malate or isocitrate via the synthetic function of the Krebs cycle; the efficiency of these reactions in cancer cells may vary. Similarly, the synthetic function of the Krebs cycle and glyceroneogenesis via oxaloacetate-PEP pathway are required for glutamine to form glycerol-3-phosphate for the biosynthesis of membrane phospholipids. The inefficiency of cells to use α-ketoglutarate as a substrate to generate NADPH and glycerol-3-phosphate could be the major reason that glutamine cannot fully compensate the lack of glucose as a carbon source in most cell types.[9] These hypotheses remain to be tested.

Theoretically, glucose may satisfy cell needs for carbon sources, but the removal of glutamine stops the growth of most types of cells in cell culture models.[9] Analysis of the key enzymes of carbon metabolic pathways revealed that glutamine starvation repressed their expression, suggesting that lack of glutamine represses the utilization of glucose.[9] Because α-ketoglutarate cannot always rescue the repressed glucose utilization caused by glutamine starvation, it is likely that the limited availability of a nitrogen source inhibits the carbon source utilization (Figure 1). How cells sense the availability of a nitrogen source and coordinately regulate carbon source utilization remains to be investigated. Particularly, the coordinated utilization of nitrogen and carbon sources in tumor cells may become a potential target for cancer management in combination with chemotherapy and radiation.

Media with high levels of glucose (20 mM), high levels of glutamine (4 mM), and high levels of oxygen (21%) represent the conventional conditions for a cell culture system, which have been used for a long time and have contributed a great deal to our current

understanding of tumor biology. However, it is noteworthy that *in vivo* tumor cells may receive much lower concentrations of glucose, glutamine, and oxygen; the physiologic ranges of glucose and oxygen in tissues are approximately 3–5 mM and 4–7%, respectively. Moreover, solid tumors usually have defective vasculature formed by angiogenesis, which further reduces the concentrations of glucose and oxygen in tumors and may also limit the availability of glutamine. Although oxygen sensing, energy sensing, adaptive mechanisms to hypoxia, and low energy status are well studied, how tumors sense low glucose status and respond to it at the cellular level remains unclear. In addition, how cancer cells interact with adjacent stromal cells *in vivo* to secure a nutrition supply remains to be fully investigated. A better understanding of the adaptive strategy of tumor cells to low glucose supply will pave a way toward better management of tumors as well as ischemic disorders where lack of glucose and energy are detrimental factors.

In conclusion, various oncogenic signaling pathways may lead to transcriptional reprogramming and metabolic reprogramming in cancer cells (Figure 2). As a result, cancer cells coordinate the utilization of carbon sources with the availability of nitrogen sources and molecular oxygen to balance the proliferative demands for ATP, redox powers, and building blocks. Furthermore, maintaining a balanced among pools of key building blocks includes mononucleotides, amino acids, heme, glycerol-3-phosphate, sphingosine, cholesterol, fatty acids, ubiquinone and polyamine is fundamental for cancer cell proliferation, which may turn out to be a novel target for future cancer therapy. The altered metabolic consequences may cause changes of the microenvironment, which further promote adaptation of cancer cells, and may eventually contribute to cancer cells' resistance to chemotherapy and radiation.

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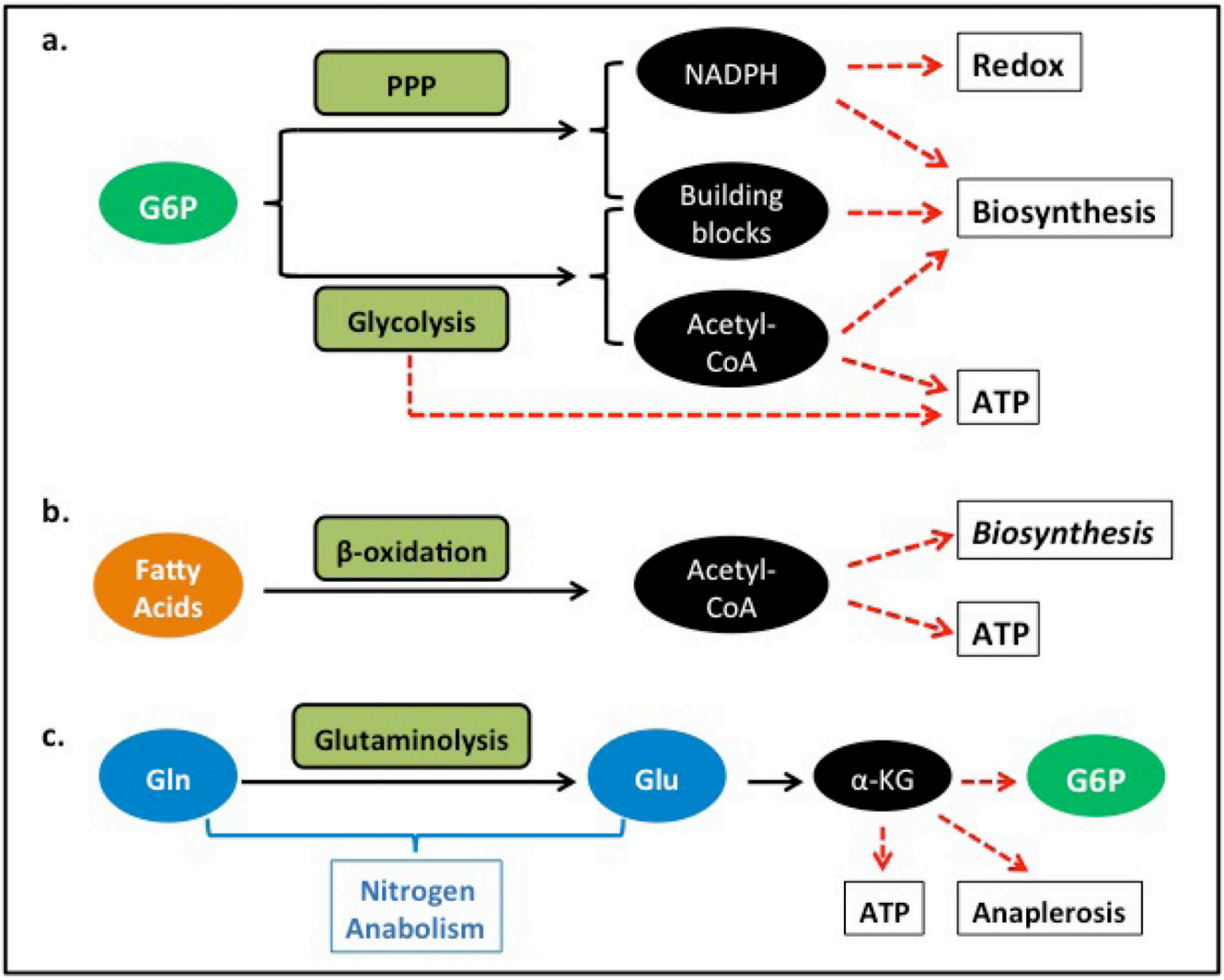

FIGURE 1.

Summary of the major types of carbon sources for cancer cells. A. Glucose is a universal carbon source that may fulfill all cell needs for carbon. Glucose-6 phosphate (G6P), derived from glucose, is the common substrate for multiple metabolic pathways. Specifically, the pentose phosphate pathway (PPP) regulated by G6PD activity is responsible for the production of NADPH, riboses, and other metabolites for biosynthesis. Glycolysis, regulated by PFK1 activity, generates pyruvate, which may be either oxidized to acetyl-CoA, or reduced to lactate. Pyruvate, acetyl CoA, and other metabolites of the glycolytic pathway can be used for biosynthesis. B. The function of fatty acids as a carbon source is limited to the generation of acetyl CoA, which can be used either for oxygen-dependent, electron transfer chain-dependent generation of ATP, or for some biosynthetic pathways. Note that fatty acids can be directly used for the biosynthesis of phospholipids. C. Glutamine (Gln) serves as a precursor of glutamate; both glutamate and glutamine have important roles in nitrogen-required anabolic pathways, including the synthesis of nucleotides, proteins, glutathione, heme, polyamines, and non-essential amino acids. Importantly, through transamination or oxidative deamination, glutamate can be converted to α-ketoglutarate (α-

KG), which links amino acid metabolism to carbon source metabolism. By entering the Krebs cycle, α-KG can be either directly oxidized as an energy source or used in anaplerotic reactions and converted to other metabolites such as malate and isocitrate, which can be used to generate NADPH. In some types of cells, α-KG can be converted to G6P through gluconeo-genesis. If the conversion of Gln to glucose is sufficiently efficient, theoretically Gin should be able to replace glucose as a universal carbon source.

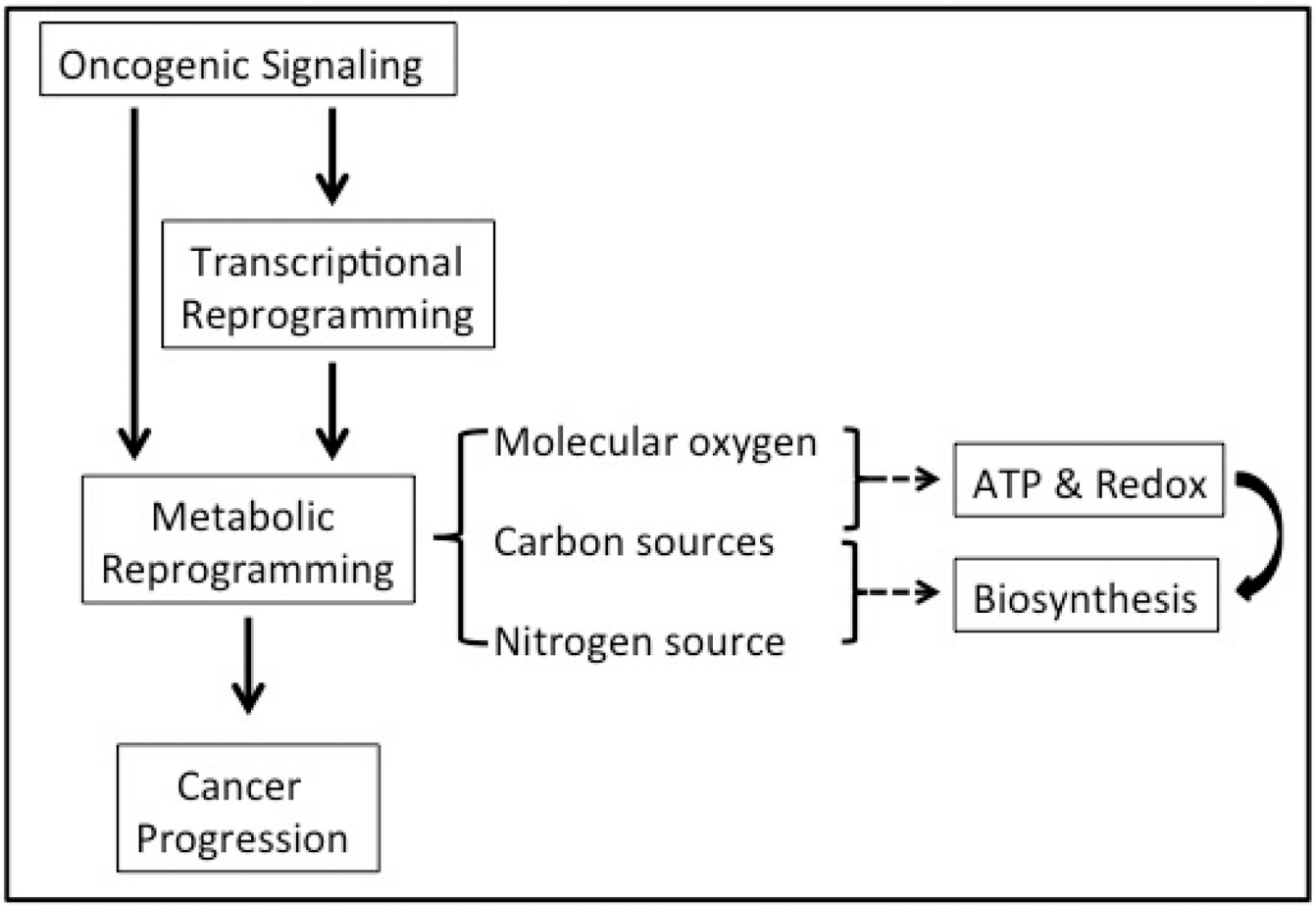

FIGURE 2.

Oncogenic signaling promotes cancer cell progression through transcriptional reprogramming and metabolic reprogramming. Based on our current understanding, oncogenic signaling pathways either directly alter the cancer cells' metabolism or indirectly modulate the enzyme expression levels through transcriptional reprogramming. Eventually, carbon sources and molecular oxygen are utilized to generate ATP, reducing power and a variety of carbon metabolites, which together support the active biosynthesis of biomass. Note that a nitrogen source, in the form of amino acids, also is required for biosynthesis of nitrogenous molecules, and its availability may limit the general cell growth and utilization of carbon sources.

TABLE 1

Currently available TB diagnostics

Glucose and glutamine update and trapping	
Glucose transporters	Updake glucose
Hexokinases	Phoshorylate glucose to G6P
Glutamine transporters	Uptake of glutamine
Glutaminases	Convert glutamine to glutamate
Glutamate dehydrogenase	Convert glutamate to α-ketoglutarate
Glutamate transaminases	Convert glutamate to α-ketoglutarate
Glycolytic ATP Production	
Phosphofructose kinase 1 (PFK1)	Glycolytic enzyme, rate limiting
Pyruvate kinase	Glycolytic enzyme, phosphoenolpyruvate (PEP) to pyruvate
Phosphofructose kinase 2 (PFK2)	Glycolysis regulator, generate F2, 6BP
Lactate dehydrogenase	Interconversion between pyruvate and lactate
Oxidative phosphorylation	
Pyruvate dehydrogenase kinase (PDK)	Repressor of pyruvate dehydrogenase complex
Pyruvate dehydrogenase complex	Pyruvate to acetyl CoA
TCA cycle enzymes	Oxidizing carbon sources, to generate NADH & FADH2
	Inter-conversion among carbon metabolites for biosynthesis
Electron transfer complexes	Pass electrons from NADH/FADH2 to molecular O2
ATP synthase	Regenerate ATP from ADP
Cytosolic NADPH production	
Glucose-6-phospate dehydrogenase (G6PD)	Pentose phosphate pathway
Malic Enzyme	NADPH: malate to pyruvate
Isocitrate dehydrogenase 1, 2	NADPH: isocitrate to α-ketoglutarate
Biosynthesis of membrane	
ATP-dependent citrate lyase	Biosynthesis: acetyl CoA generation in cytosol
Acetyl CoA carboxylase (ACC)	Fatty acid synthesis: acetyl CoA to malonyl CoA
Fatty acid synthase (FASN)	Fatty acid synthesis: multiple activities, synthesize palmitate
HMG-CoA reductase	Cholesterol biosynthesis: HMG-CoA to mevalonate
Glycerol kinase	Phospholipid biosynthesis: glycerol to glycerol-3
Glycerol-3-phosphate dehydrogenase (GPDH)	Phospholipid biosynthesis: DHAP to glycerol-3P
Phosphoenopyruvate carboxylkinases (PEPCK)	Convert oxalocaetate to PEP to DHAP to glycerol-3P
Acyl CoA transferases	Phospholipid biosynthesis: link fatty acid to glycerol-3P
Diacylglycerol (DAG) kinase	Phospholipid biosynthesis: DAG to phosphatidic acid
Serine C-palmitoyltransferases	Sphingosine biosynthesis
Biosynthesis of other important metabolites for biosynthesis	
Pyruvate carboxylase	Convert pyruvate to oxaloacetate
Phosphoglycerate dehydrogenase (PHGDH)	Serine synthesis: 3-P-glycerate to 3-P-hydroxypyruvate

Serine hydroxymethyltransferase (SHMT)	Produce glycine and methylenetetrahydrofolate
Dihydrofolate reductase (DHFR)	Reduce dihydrofolate to tetrahydrofolate

TABLE 2

Major Metabolic Enzymes Up-regulated by HIF-1

Genes		Swiss Prot	Reference
Slc2a1	Glucose transporter 1	P11167	119
HK2	Hexokinase 2	P52789	120
Ldha	Lactate dehydrogenase A	P06151	121
PDK1	pyruvate dehydrogenase kin; ase 1	Q15118	40
CAIX	carbonic anhydrase IX	Q8VHB5	42
MCT4	Monocarboxylate transporter4	Q15427	41

TABLE 3

Major Metabolic Enzymes Up-regulated by c-Myc

Genes		Swiss Prot	Reference
Slc2a1	Glucose transporter 1	P11167	47
HK2	Hexokinase 2	P52789	46
Ldha	Lactate dehydrogenase A	P06151	45
PDK1	Pyruvate dehydrogenase kinase 1	Q15118	46
Pfkl	Phosphofructokinase (PFK1)	P30835	47
Eno1	Enolase 1	P04764	47

TABLE 4

Target Genes Up-regulated by MondoA:Mlx Complex

Genes		Swiss Prot	References
Carbon metabolism			
Hk2	Hexokinase 2	O08528	122
Ldha	Lactate dehydrogenase A	P06151	122
Pfkfb3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	Q7TS91	122
Redox-related protein			
TXNIP	Thioredoxin-interacting protein	Q9H3M7	93

TABLE 5

Target Genes Regulated by MondoB:Mlx Complex

Genes		Swiss Prot	References
Carbon metabolism			
Slc2a4	Glucose transporter 4	P19357	100
Gckr	Glucokinase regulatory protein	Q07071	100
Pklr	Liver-type pyruvate kinase	P12928	98
Gpd1	Glycerol-3-phosphate dehydrogenase 1	O35077	100
Acaca	Acetyl-CoA carboxylase 1	P11497	123
Fasn	Fatty acid synthase	P12785	124
Gpam	Glycerol-3-phosphate acyltransferase 1, mitochondrial		125
Metabolic regulators			
G0S2	G0/G1 switch gene 2	Q5M840	100
Thrsp	Thyroid hormone-inducible hepatic protein	P04143	124
Fgf21	Fibroblast growth factor 21	Q8VI80	100, 126
Ppara[*]	Peroxisome proliferator-activated receptor á	P37230	127
Arnt[*]	Aryl hydrocarbon receptor nuclear translocator	P41739	128
Redox-related protein			
TXNIP	Thioredoxin-interacting protein	Q9H3M7	129

[*] Ppara and Arnt are down-regulated by the MondoB:Mlx complex. All other genes are up-regulated.