MYC-Induced Cancer Cell Energy Metabolism and Therapeutic Opportunities

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Abstract Although cancers have altered glucose metabolism, termed the Warburg effect, which describes the increased uptake and conversion of glucose to lactate by cancer cells under adequate oxygen tension, changes in the metabolism of glutamine and fatty acid have also been documented. The MYC oncogene, which contributes to the genesis of many human cancers, encodes a transcription factor c-Myc, which links altered cellular metabolism to tumorigenesis. c-Myc regulates genes involved in the biogenesis of ribosomes and mitochondria, and regulation of glucose and glutamine metabolism. With E2F1, c-Myc induces genes involved in nucleotide metabolism and DNA replication, and microRNAs that homeostatically attenuate E2F1 expression. With the hypoxia inducible transcription factor HIF-1, ectopic c-Myc cooperatively induces a transcriptional program for hypoxic adaptation. Myc regulates gene expression either directly, such as glycolytic genes including lactate dehydrogenase A (LDHA), or indirectly, such as repression of microRNAs miR-23a/b to increase glutaminase (GLS) protein expression and glutamine metabolism. Ectopic MYC expression in cancers, therefore, could concurrently drive aerobic glycolysis and/or oxidative phosphorylation to provide sufficient energy and anabolic substrates for cell growth and proliferation in the context of the tumor microenvironment. Collectively, these studies indicate that Myc-mediated altered cancer cell energy metabolism could be translated for the development of new anticancer therapies. (Clin Cancer Res 2009;15(21):6479–83)

Background

The *MYC* gene has long been known to be altered by chromosomal translocations and gene amplification in human cancers. In addition, common single nucleotide polymorphisms (SNP) on human chromosome 8q24, which predispose to colon, breast, prostate, and bladder cancers, have been implicated in deregulated MYC expression (1). The region containing 8q24 SNP rs6983267 confers increased cancer risk (odds ratio ~ 1.5) and is located >300 kb away from *MYC* (2). This SNP contributes to a consensus TCF4 binding site and has features of a long-distance regulatory sequence or enhancer that is tethered to the *MYC* promoter via DNA looping. Therefore, this SNP could increase *MYC* expression through TCF4 generated by activation of the WNT signaling pathway. In this regard, subtle changes in deregulated *MYC* expression can have a profound effect on tumorigenesis in animal models (3). *MYC* is, hence, central to the genesis of most commonly occurring human cancers (Fig. 1).

Given the central role of *MYC* in many human cancers, it is critical that the c-Myc (herein termed Myc) transcription factor be well-understood, particularly in its role in stem cell maintenance and tumorigenesis (4–6). Myc is a helix-loop-helix leucine zipper transcription factor that dimerizes with its partner protein Max to bind specific DNA sequences and transactivates genes. The Myc-Max heterodimer can also repress gene expression through complex formation with the transcription factor Miz1 (5). In addition to its role in cancer, Myc is one of four transcription factors that collectively can re-program differentiated adult cells back to a pluripotent stem cell state (7).

In addition to its role in cancer, Myc also plays an important role in normal cell physiology. The key distinction between physiological and oncogenic Myc function is whether *MYC* expression is regulated by normal circuitries, such as growth factor signaling that occurs when cells enter into the cell cycle and proliferate for tissue repair, or whether, as in cancers, *MYC* activation can be short-circuited by genetic alterations, permitting deregulated Myc expression to alter transcription that no longer responds to external cues, particularly negative regulatory ones (8). Ectopic Myc expression is normally kept in check by its activation of p53 or Arf, which triggers apoptosis, senescence, or cell cycle arrest. In this regard, Myc-mediated lymphomagenesis requires p53 or Arf loss of function (9). It has been of major interest to understand the transcriptional program, particularly, downstream of deregulated Myc expression. To this end, many

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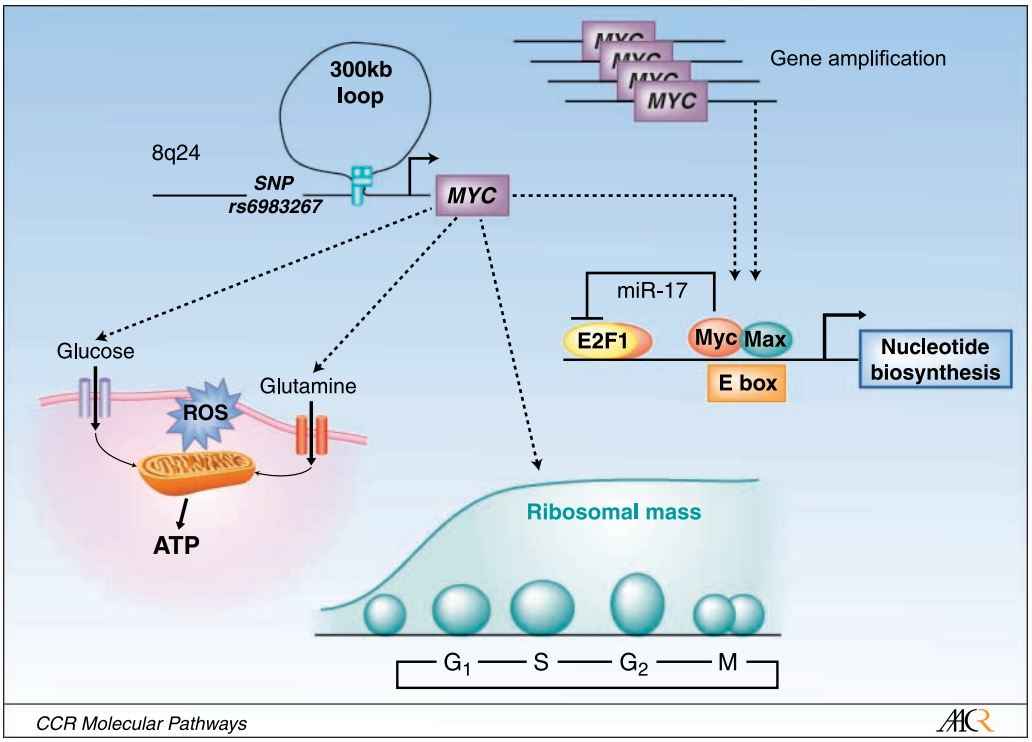

Fig. 1. Altered MYC expression and Myc function. Cancer predisposing SNP r6983267 located >300 kb away is shown tethered to the MYC promoter, altering its expression. MYC gene amplification, which is found in some human cancers, is also illustrated. Myc in turn regulates energy metabolism and ribosomal biogenesis, which provides the bulk of cellular mass through the cell cycle. As cells enter S phase, Myc together with E2F1 regulates nucleotide metabolism with a negative regulatory loop involving miR-17 that attenuates E2F1 protein levels for safe passage through DNA replication.

laboratories have recently used high throughput methods to map the Myc target gene network (4, 5).

Intriguingly, multiple studies have shown that Myc can directly bind the promoters of thousands of genes, as high as 30% of all known genes, but only a fraction of the bound genes actually respond (up-regulated or down-regulated) to Myc (10–13). Myc-mediated transcriptional regulation requires other cooperating transcription factors to regulate target genes (10, 11, 14). For example, Myc cooperates with other stem cell transcription factors to regulate genes found in embryonic stem cells (15). Myc cooperates with E2F1 to regulate genes involved in nucleotide metabolism and with the hypoxia inducible factor 1 (HIF-1) to regulate genes involved in glucose metabolism (11, 16, 17).

The key lesson learned from lower organisms and mammals is that whereas Myc regulates a myriad of genes, a conserved core set of Myc target genes seems to be involved in ribosomal and mitochondrial biogenesis, energy metabolism, and regulation of cell cycle (Fig. 1). Direct mapping of dMyc target genes in *Drosophila* identified CDK4 (18), which was also independently confirmed in mammalian cells as a direct Myc target, thereby linking Myc to cell cycle regulation across species (19). Mutant flies with diminished dMyc function have small cell and body size that pheno-copies mutants with loss of ribosomal protein function, linking Myc to ribosomal biogenesis (20). The finding that Myc could regulate transcription mediated by RNA polymerases I (for rRNA transcription) and III (for tRNA and small RNA transcription), in addition to RNA Pol II, further shows its role in biogenesis of ribosomes (4, 5, 21). Studies in multiple mammalian systems document a role for Myc in the regulation of genes involved in mitochondrial biogenesis and function, such that increased Myc function is associated with enhanced mitochondrial mass and function (22–25). These studies collectively indicate a key role for Myc in organellar biogenesis that is required for energy production, biosynthesis, and cell growth.

Clinical Translational Advances

The role of Myc in cancer energy metabolism. Deregulated MYC expression is found in many commonly occurring human cancers including colon, breast, prostate, and bladder cancer. It is estimated that increased *MYC* expression contributes to the cause of at least 40% of all human cancers.[1] Early studies established Myc as a transcription factor through the identification of the transactivation domain and specific DNA binding domain (26–28). Subsequent studies of Myc target genes focused on its role in the regulation of the cell cycle, because the genesis of cancers was thought to reside mainly in a deregulated cell cycle machinery. In fact, Myc seems to play a role in DNA replication distinct from its role as a transcription factor (29). The link between Myc and regulation of glucose metabolism was first established when an early unbiased screen for Myc target genes uncovered lactate dehydrogenase A (LDHA) among 20 other putative Myc target genes (30, 31). LDHA converts pyruvate, which is derived from glucose through glycolysis or other sources, to lactate (Fig. 2).

Many other glucose metabolism genes were subsequently documented to be directly regulated by Myc. Chief among these are the glucose transporter *GLUT1*, hexokinase 2 (*HK2*), phosphofructokinase (*PFKM*), and enolase 1 (*ENO1*; refs. 32–34). Myc is hence able to stimulate genes that increase the transport of glucose, its catabolism to trioses and pyruvate, and ultimately to lactate (Fig. 2). Because glycolytic genes are also directly responsive to HIF-1, the interplay between Myc and HIF was documented through genes that could be regulated by

[1] http://www.myccancergene.org

both transcription factors (17). Collectively, these studies suggest that HIF-1 transactivates glucose transporter and glycolytic genes in common with Myc; HIF-1 transactivates these genes under hypoxic conditions (anaerobic glycolysis), whereas Myc regulates the same set of genes under nonhypoxic conditions. These observations imply that Myc could contribute to the Warburg effect (aerobic glycolysis) or the ability to convert glucose to pyruvate and in turn to lactate even under adequate oxygen tension.

The ability of Myc to transactivate genes involved in glycolysis under normal oxygen tension begged the question of whether pyruvate, which is converted to lactate by LDHA, could also be converted to acetyl-CoA and oxidized by increased Myc-mediated mitochondrial biogenesis. In this regard, Li and colleagues documented that genes involved in mitochondrial biogenesis and function are statistically over-represented among Myc target genes (23). They further document through gain-of-function and loss-of-function analysis of Myc, that mitochondrial mass and function correlate with Myc function, a link that was suggested earlier and has since been corroborated by additional studies (22, 24, 25).

Myc not only induces genes that convert glucose to lactate but also those conferring mitochondrial oxidation of substrates via the tricarboxylic acid (TCA) cycle. What then would happen to glucose metabolism in hypoxic Myc-transformed cancer cells? In this regard, Kim and colleagues screened for genes that might be in common to Myc and HIF-1 under hypoxic conditions (32, 33, 35). They found that PDK1, encoding pyruvate dehydrogenase kinase 1, was robustly transactivated by HIF-1 and further increased by Myc (Fig. 2). They further documented that PDK1, which blocks the conversion of pyruvate to acetyl-CoA by phosphorylation of pyruvate dehydrogenase, inhibits mitochondrial oxidation of pyruvate under hypoxic conditions (35). These observations suggest that Myc could stimulate glucose oxidation and lactate production in normoxia. Under hypoxia, Myc collaborates with HIF-1 to induce PDK1, thereby suppressing mitochondrial respiration and favoring the conversion of glucose to lactate. Decreased expression of PDK1 mediated by siRNA under hypoxic conditions was accompanied by cell death because of oxidative stress from continued mitochondrial respiration under low oxygen tension. Concurrent studies of Papandreou and colleagues (36) corroborated the significance of these observations, which are underscored by the fact that inhibition of PDK1 by dichloroacetate decrease tumor growth in a xenograft model of lung carcinoma (37).

Because Myc is able to induce mitochondrial biogenesis and oxygen consumption in human B cels, Gao and colleagues sought to determine the effects of Myc on their mitochondrial proteome (38). Through proteomic analysis of mitochondria from high Myc-expressing human B lymphocytes as compared with control lymhocytes, mitochondrial glutaminase (GLS) was among seven proteins identified with >10fold induction by Myc. Further analyses revealed that unlike glutamine transporters (ASCT2 and SLC7A25), which are direct Myc target genes, GLS protein level was induced by Myc through direct suppression of microRNAs miR-23a and miR-23b, which target the GLS mRNA 3′-UTR. GLS is the first enzyme that converts glutamine to glutamate, which is in turn converted to α-ketoglutarate for further metabolism in the TCA cycle (Fig. 2). It is notable that Myc-overexpressing human cell lines were found to be dependent on glutamine, such that its withdrawal triggered apoptosis (39). Furthermore, independent studies by Wise and colleagues also documented that Myc induces genes involved in glutamine metabolism to confer glutamine-addiction (40). With adequate oxygen tension, α-ketoglutarate derived from glutamine could then be oxidized through the TCA cycle, indicating that Myc can induce glutamine oxidation concurrently with aerobic glycolysis. Studies of a glioblastoma cell line indicate that glutamine can also be converted to lactate through glutaminolysis (41), which was recognized several decades ago as a major mode of glutamine metabolism in certain cell lines (42).

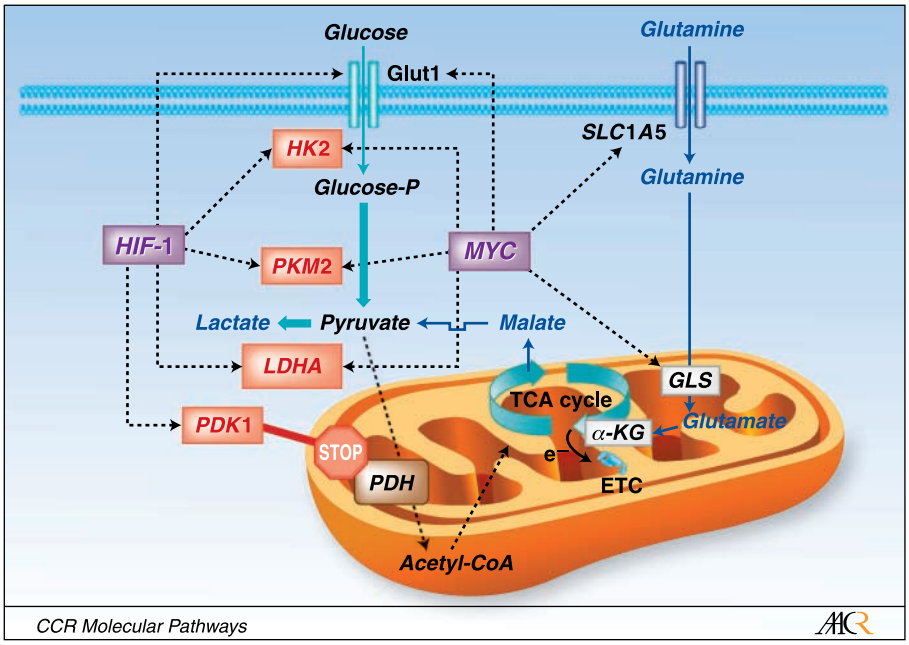

Fig. 2. Myc and HIF-1 regulate glucose metabolism and stimulate the Warburg effect. Myc and HIF-1 are depicted to regulate (dotted lines) genes involved in glucose metabolism (glucose transporter Glut1, HK2, PKM2, LDHA, and PDK1), favoring the conversion of glucose to lactate (glycolysis). Myc is also depicted to stimulate glutamine metabolism through the regulation of transporters (SLC1A5) and glutaminase (GLS). Glutamine is shown converted to α-ketoglutarate (α-KG) for catabolism through the TCA cycle to malate, which is transported into the cytoplasm and converted to pyruvate and then to lactate (glutaminolysis). High energy electrons (e^-) from the TCA cycle is shown transported with the electron transport chain (ETC). PDH, pyruvate dehydrogenase.

Glutaminolysis involves lactate production from the conversion of glutamine to α-ketoglutarate, which is in turn catabolized through part of the TCA cycle to malate and then transported out of the mitochondrion (Fig. 2). Cytoplasmic malic enzyme converts malate to pyruvate with the concomitant production of NADPH from $NADP^+$ (43). Pyruvate is then converted to lactate by LDHA. Although a portion of lactate is produced from glutamine in selected cancer cell lines *in vitro* (41, 44), the context when glutaminolysis plays a role in cancer metabolism *in vivo* remains to be established. Notwithstanding these caveats, Myc is able to induce the expression of genes involved in both glycolysis and glutaminolysis with LDHA being critical for both processes.

Cancer Cell Metabolism and Therapeutic Opportunities

In addition to the induction of glucose and glutamine metabolic enzyme genes, Myc also induces genes involved in nucleotide metabolism and polyamine synthesis. With E2F1, Myc regulates genes involved in nucleotide metabolism and DNA replication, as well as microRNAs that homeostatically attenuate E2F1 expression for safe passage of cells through S phase (11, 45–47). Interference with this microRNA (miR-17 cluster) circuitry results in DNA replication stress (48). Nucleotide metabolism has been a key target for cancer therapeutics over the last 50 years, culminating in many agents, such as 5-fluorouracil and nucleosides that are part of the current therapeutic armamentarium. The new understanding that an important oncogene directly regulates multiple metabolic pathways suggests that new opportunities exist, particularly in altered cancer energy metabolism.

A number of small organic molecules have been reported to target glycolysis, but none to date has been shown to have specific molecular targets. For example, 3-bromopyruvate, a highly active akylating agent, is reported to target HK2, but to date little biochemical evidence is available to support this claim (49). In fact, recent studies have implicated GAPDH as a potential target of 3-bromopyruvate (50). Although 2-deoxyglucose can be phosphorylated by HK2 and in turn inhibit HK2, it has nonglycolytic effects (51). Other attractive targets for therapy include pyruvate kinase M2 (PKM2), which converts phosphoenolpyruvate to pyruvate (52–54) and LDHA, because three independent studies have shown that loss of LDHA function results in dramatically diminished cellular transformation or xenograft tumor growth (31, 55, 56).

Upon its identification as a direct Myc target in 1997, antisense-mediated suppression of LDHA expression in several human lymphoid tumor cell lines markedly decreased soft agar colony growth (31). This study also suggested that LDHA is necessary for adaptation to hypoxia resulting from growth of spheroid cellular masses in soft agar. Indeed, Fantin and colleagues later showed that stable interference RNA (shRNA) mediated knock-down of LDHA expression in mouse mammary tumor cells, which resulted in prolonged survival of tumor inoculated animals as compared with those inoculated with control cells (55). They also documented that decreased LDHA expression was associated with increased mitochondrial respiration, but neither the effect on reactive oxygen species (ROS) production nor the mechanism for cellular toxicity due to lowered LDHA expression was reported. Similar to PDK1 inhibition, which enhances pyruvate oxidation in hypoxia and ROS, lowered LDHA expression could also result in oxidative stress and ensuing apoptosis. More recently, shRNA mediated knock-down of LDHA in a lung carcinoma xenograft model was also documented to inhibit tumor xenograft growth (56). In aggregate, these studies provide proof-of-concept that targeting LDHA could be a fruitful avenue, particularly because humans genetically lacking LDHA are viable and normal except for exercise-induced myoglobinuria. Our preliminary studies suggest that small organic molecules capable of inhibiting human LDHA (57) could inhibit *in vivo* xenograft tumor growth of human B lymphoid tumor and pancreatic cancer cells, paving the way for further development of therapeutic LDHA inhibitors.[2]

As discussed, glutamine metabolism is an important pathway regulated by Myc and glutaminase was documented to be required for the proliferation of human B lymphoid tumor cells and the prostate PC3 cancer cell lines, suggesting that it could be a key target for therapy (38). Furthermore, antisense reduction of glutaminase expression diminishes the *in vivo* tumorigenicity of Erhlich ascites tumor (58, 59). In this regard, it is notable that the antileukemic effect of L-asparaginase in childhood acute lymphocytic leukemia is due to the associated glutaminase activity, which diminishes circulating glutamine levels and deprives leukemic cells of a major energy and anabolic substrate (60). Unfortunately, 6-diazo-5-oxo-*l*-norleucine (DON) and acivicin, which are both glutamine analogs, have been met with significant central nervous system (CNS) side effects (61). Glutamine is taken up by neurons and converted by glutaminase to glutamate, a major neurotransmitter, which is released into the synaptic cleft and then rapidly cleared to prevent prolonged, toxic neuronal stimulation. In this regard, specific inhibitors of glutaminase or glutamate dehydrogenase may prove to be more useful for non-CNS cancers if the inhibitors could not cross the blood brain barrier (62).

Conclusions

The molecular biology revolution has taken modern cancer biology from the discovery of oncogenes and tumor suppressors back to the past with direct links of these genetic alterations to altered cancer cell metabolism, which was first described by Otto Warburg more than 80 years ago. In this regard, Myc-mediated alterations in glucose and glutamine metabolism provide fertile ground for the development of a new class of anticancer drugs, which are likely to emerge in the clinics over the next 5 to 10 years.

Disclosure of Potential Conflicts of Interest

C.V. Dang, consultant, Agios Pharmaceuticals, Inc. The other authors report no conflict of interest.

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[2] A. Le and C.V. Dang, unpublished observations.

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