Chapter 5
MYC Regulation of Metabolism and Cancer

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5.1 Introduction

The field of cancer metabolism has grown rapidly over the last decade as more links between oncogenes and metabolism are uncovered 90 years after Otto Warburg made his seminal observations that many cancers consume vast amounts of glucose and convert it to lactate (Vander Heiden et al. 2009; Koppenol et al. 2011; Cantor and Sabatini 2012). To grow, proliferate, and survive, cancer cells exhibit different metabolic programs including the Warburg effect. However, the Warburg effect per se is insufficient to provide cancer cells with all the substrates for growth and survival. In the past decade, many genetic changes in cancers have been linked to the Warburg effect, glutaminolysis, carbohydrate, and fatty acid metabolism. Among the genetic alterations, oncogenic MYC stood out as a canonical oncogene that was first to be linked mechanistically to altered glucose metabolism, when it was discovered to transactivate *LDHA*, encoding lactate dehydrogenase A (Shim et al. 1997). MYC is now known to amplify the expression of thousands of genes, with the bulk involved in various aspects of cell metabolism including glycolysis, glutaminolysis, nucleotide, protein, and fatty acid metabolism (Dang 2012). MYC is also involved in mitochondrial and ribosome biogenesis. ln this chapter, we will provide an overview of key roles of MYC in regulating metabolism and how they contribute to cancer development and progression.

5.2 MYC and Cancer

Cell growth or the increase in cell mass required for cell proliferation involves the import of nutrients and their conversion to cell mass and ATP. MYC and the mTOR pathway are critical for cell growth. Discovery of the retroviral v-MYC oncogene (Duesberg and Vogt 1979) led to the identification of its cellular homologue termed c-MYC (Vennstrom et al. 1982). Herein, the human gene will be termed *MYC* (italicized) and the protein termed MYC. The normal proto-oncogene *MYC* is downstream of many growth factor signaling pathways, including receptor tyrosine kinase pathway, T cell receptor pathway, and WNT signaling pathways that regulated its expression through sensing extracellular cues (Dang 2012). The *MYC* proto-oncogene is a member of the *MYC* family, which includes *MYCN* and *MYCL*. While *MYCN* is commonly amplified in neuroblastoma, an aggressive childhood cancer, *MYCL* is only occasionally amplified in some human small cell lung cancer (Brodeur et al. 1984; Nau et al. 1985).

The *MYC* proto-oncogene is activated by chromosomal translocations in human Burkitt's lymphoma (Dalla-Favera et al. 1982; Taub et al. 1982). The juxtaposition of *MYC* to one of three immunoglobulin enhancers via chromosomal translocations deregulates its expression. *MYC* is now found to be one of the most frequently amplified human oncogene among many different types of cancers, illustrating its central role in human cancer development (Beroukhim et al. 2010; Atlas 2012a, b;

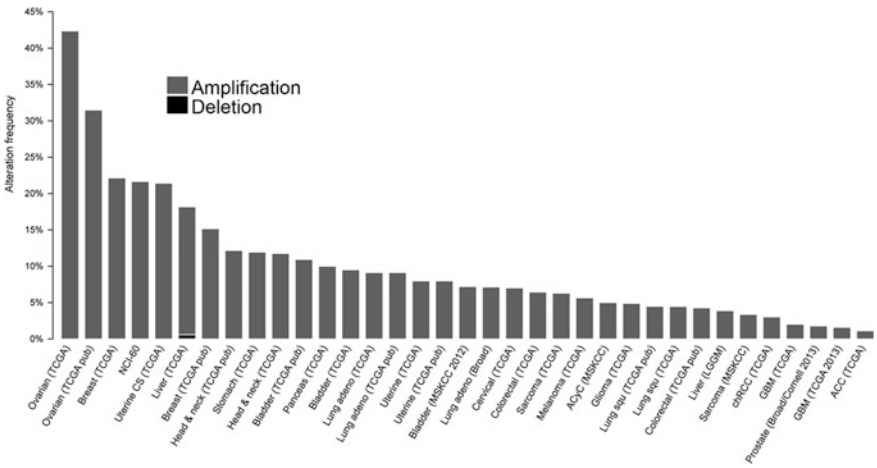

Fig. 5.1 MYC alterations in human cancer and cancer cell lines. TCGA data are displayed through cBioPortal. Note that MYC is largely amplified across multiple human cancers

Cancer Genome Atlas Research N 2012; Cancer Genome Atlas Research N et al. 2013) (Fig. 5.1).

Furthermore, loss of upstream regulators such as APC in the WNT pathway can also lead to deregulated *MYC* gene expression in cancers (Beroukhim et al. 2010; He et al. 1998). In addition to its important role in cancer, *MYC* plays a pivotal role in maintaining the pluripotency of stem cells (Varlakhanova et al. 2010). Notably, MYC is also one of the four transcription factors that can induce pluripotency in human skin fibroblast (Takahashi and Yamanaka 2006). These observations suggest that MYC's contribution to cellular dedifferentiation might be central to its neoplastic transforming activity.

Given its important role in growth, *MYC* expression is tightly regulated in non-transformed cells such that its acute overexpression results in activation of cell cycle checkpoints such as ARF and p53 (Dang 2012). Hence in normal cells, overexpressed MYC leads to cell growth arrest or apoptosis. Unlike their normal counterparts, many cancers with deregulated MYC lose these checkpoints such as loss of p53 in human Burkitt's lymphoma (Schmitz et al. 2012, 2014).

The role of MYC in tumorigenesis has been extensively studied in a number of human cell lines and transgenic mouse models. While overexpression of MYC in cells that have lost checkpoints results in tumorigenesis, loss of MYC can trigger cell death in a Burkitt's lymphoma model cell line with a tetracycline-regulated MYC transgene (Yustein et al. 2010). Activation of an MYC transgene specifically in the liver of a mouse model induced the formation of large liver tumors, which also exhibited the so-called oncogene addiction. Being addicted, these tumors regressed upon silencing of the MYC transgene (Felsher 2010). These findings suggest that MYC is important in tumor initiation and maintenance. Once these tumors are established, they can also be addicted to MYC, perhaps partially via the

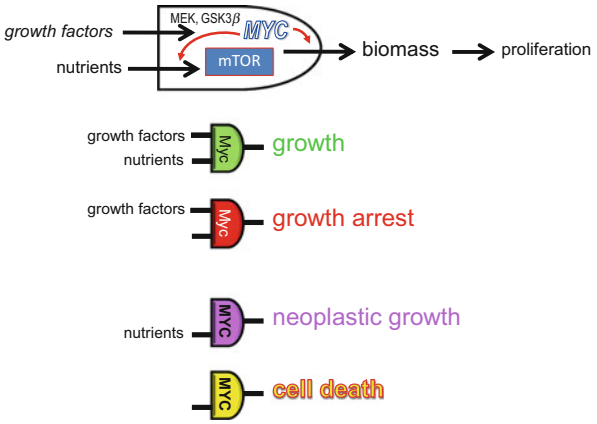

Fig. 5.2 MYC proto-oncogene mediates a transcriptional program that provides nutrients for the cell and stimulates it to grow. In normal cells, it is surmised that growth factors and nutrients are both required for cell proliferation, such that nutrient deprivation will result in diminished (lowercase MYC) MYC expression leading to growth arrest

metabolic pathways that MYC regulates. Indeed, we hypothesize that deregulated MYC results in deregulated cell growth signaling that requires a commensurate constitutive source of bioenergetic nutrients, such that the MYC-transformed cell becomes addicted to glucose, glutamine, and other nutrients (Fig. 5.2). In this regard, we will review in this chapter the connections between MYC, cell growth, proliferation, and metabolism as they are related to cancer biology and therapy.

5.3 Function of MYC

MYC protein is composed of a transactivation domain at N-terminal and a helix-loop-helix leucine zipper domain at C-terminal for DNA binding (Baudino and Cleveland 2001). Upon induction, MYC heterodimerizes with its partner MAX, which is also a helix-loop-helix leucine zipper protein, to bind the consensus DNA sequence (CACGTG or E-box) or its variants and alter gene expression (Dang 2012).

The oncoprotein MYC has many binding targets, perhaps up to 15 % of genes (Fernandez et al. 2003; Cawley et al. 2004). Global mapping of MYC binding sites in the human genome using human Burkitt's model lymphoma cells had demonstrated that approximately 3,000 genes are associated with MYC (Zeller et al. 2006). Among these 3,000 MYC-bound genes, 688 that were found to have altered are involved in protein synthesis and cell metabolism, suggesting that MYC activates metabolic reprogramming in cancer cells to fulfill the increased metabolic needs required for rapid growth. Subsequent global mapping of MYC binding sites has broadened the number of putative MYC targets, but expression analysis shows that many key metabolism genes are among the most upregulated genes.

Recent studies have suggested that MYC is a universal amplifier of gene expression through the release of RNA Pol II promoter pausing (Lin et al. 2012; Nie et al. 2012). However, MYC does not uniformly upregulate all genes to the

same degree, suggesting that there is a hierarchy to global MYC regulation. That is, MYC regulates specific genes to different degrees depending on their specific cellular function. For example, MYC would not amplify tumor suppressor genes to the same extent as it would amplify the expression of growth-promoting genes in a cell stimulated to grow. Further, these observations could not explain MYC-mediated suppression. For instance, a few studies showed that MYC suppresses cyclin-dependent kinase inhibitors p15 and p21 by recruiting Miz-1 (Seoane et al. 2001, 2002; Staller et al. 2001). For cancer cells to proliferate, the balance between the expression of growth-promoting genes and growth-arresting genes needs to be maintained.

5.4 Role of MYC in Cell Growth and Proliferation

MYC consistently alters specific groups of genes that are involved in metabolism, protein biosynthesis, cell cycle regulation, angiogenesis, and apoptosis (Prendergast 1999; Nilsson and Cleveland 2003; Baudino et al. 2002). We will not discuss all of MYC's target genes, but three functions relevant to cancer proliferation stand out: cell cycle, protein synthesis, and metabolism. While these roles of MYC have been studied separately, these processes are inextricably linked with metabolism, fueling MYC-driven cell growth and proliferation.

MYC has been shown to drive the cell cycle through E-box-dependent promoter regulation of cyclins D1 and D2, *CDK4*, and cyclin B1 (Fernandez et al. 2003; Bouchard et al. 2001; Menssen and Hermeking 2002; Hermeking et al. 2000). Via inhibiting Miz1, MYC can enhance the cell cycle through repression of CDK repressors p21 and p151NK4A (Wu et al. 2003; Seoane et al. 2001).

Cell cycle progression requires that cells attain a certain cell size before initiating DNA replication and the ensuing cell division to produce two daughter cells. In addition to accelerating the progression of the cell cycle, MYC also accelerates protein synthesis and increases cell size. Indeed, MYC overexpressing fibroblasts show protein synthesis that is about threefold higher than in *MYC* knockout fibroblasts (Mateyak et al. 1997). MYC plays a key role in regulating ribosome biogenesis (Kim et al. 2000; Schlosser et al. 2003; Poortinga et al. 2004). Studies have also shown that *Drosophila* mutants for these ribosomal protein genes have smaller body size which phenocopies a natural *Drosophila* MYC mutant fly, termed diminutive (Orian et al. 2003; Fernandez et al. 2003). Conversely, overexpressing MYC in *Drosophila* (which is called dMYC) increases their cell size, thus increasing the size of body parts (when dMYC is expressed in a tissue-specific fashion) (de la Cova et al. 2004; Moreno and Basler 2004; Secombe et al. 2004). Not only do dMYC-overexpressing cells grow bigger, but they competitively induce apoptosis on their surrounding cells which have lower levels of dMYC (de la Cova et al. 2004). In vertebrates, overexpression of MYC in the liver caused liver hypertrophy (Kim et al. 2000) and in B cells caused enlarged lymphocytes (Iritani et al. 2002). MYC is unique among transcription factors in that it can activate

transcription mediated by all three RNA polymerases I, II, and III to drive ribosomal biogenesis and protein synthesis (Gomez-Roman et al. 2003). MYC binds to pol III-transcribed tRNA and 5S rRNA promoter genes which all play a major role in protein synthesis. MYC also directly stimulates rRNA transcription (Arabi et al. 2005; Grandori et al. 2005; Grewal et al. 2005). All these studies suggest several ways by which MYC increases cell size via ribosome biogenesis and protein synthesis. Taken together these studies show that MYC increases cell size and protein synthesis by driving ribosome synthesis, necessitating the increased uptake or synthesis of nucleotides and amino acids. Below we will discuss how MYC reprograms metabolism to work hand in hand with cell cycle and ribosome biogenesis to drive cancer cell growth and proliferation.

5.5 MYC and Metabolism

Cancer cells exhibit profound metabolic changes, promoting the synthesis of cellular building blocks to support cellular growth, proliferation, and survival (Ward and Thompson 2012). Cancer cells must produce sufficient lipids and phospholipids to build cellular and organelle membranes and sufficient nucleotides to replicate DNA, increase mRNA and build ribosomes, and acquire and produce sufficient amino acids to fuel protein synthesis.

The most noted change in cancer metabolism has been aerobic glycolysis or the Warburg effect, first noted by Otto Warburg in his landmark studies beginning in the 1920s (Koppenol et al. 2011; Warburg et al. 1927). In contrast to non-cancer cells where pyruvate derived from glucose via glycolysis enters the mitochondria and is oxidatively metabolized to maximize ATP production, proliferating cancer cells primarily convert pyruvate to lactate even in the presence of oxygen. Although aerobic glycolysis sacrifices ATP production per molecule of glucose, the increase of glucose flux in aerobic glycolysis provides the opportunity for cancer cells to maximize cellular building blocks via shunting of glycolytic intermediates into biosynthetic pathways. Glycolytic intermediates provide fuel for the pentose phosphate pathway, which provides ribose or nucleotide synthesis and NADPH for cellular reducing power; the serine biosynthesis pathway, which plays a critical role in nucleotide synthesis; and glycerol, which plays a key role in triglyceride metabolism (Ward and Thompson 2012).

In addition to glucose metabolism, cancer cells show additional metabolic changes. Many cancer cells become markedly dependent on glutamine for glutathione, protein, and nucleotide synthesis. Cancer cells often boost nucleotide metabolism, upregulating the synthesis of purine and pyrimidines to support DNA and RNA synthesis. Additionally, cancer cells reprogram how they synthesize and take up nonessential and essential amino acids.

One of the great advances in our understanding of cancer metabolism over the last 15 years is relationship between the recurrent genetic changes observed in cancer and the metabolic phenotypes of the resultant cancers. The p53 protein, one

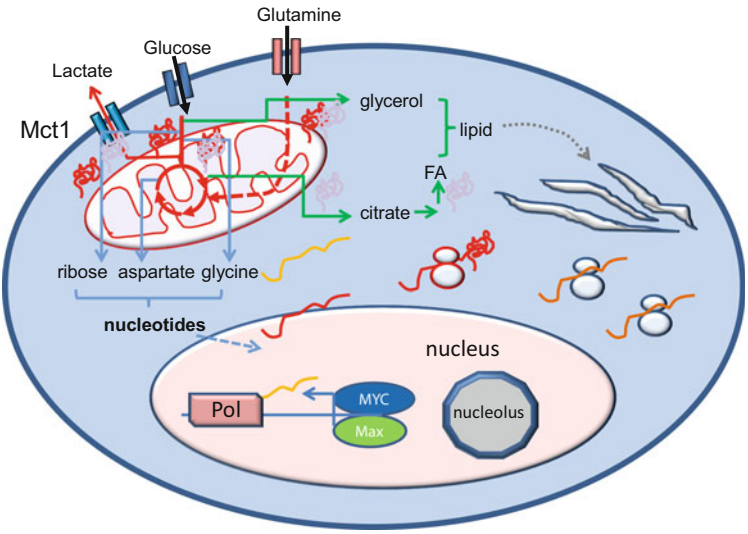

Fig. 5.3 MYC stimulates genes involved in glycolysis, glutaminolysis, lipid, and amino acid synthesis as well as mitochondrial and ribosomal biogenesis. Glucose and glutamine are depicted to be transported and catabolized through glycolysis and the mitochondrion to produce ATP and the building blocks for nucleotide, lipid, and protein synthesis. The mitochondrion is depicted as a central biosynthetic organelle in addition to its function in oxidative phosphorylation. *FA* fatty acid, *MCT1* monocarboxylate transporter 1

of the most frequently mutated or lost genes in cancer, has been shown to be a key regulator of glucose, glutamine, and amino acid metabolism (Bensaad et al. 2006; Hu et al. 2010; Jiang et al. 2011; Maddocks et al. 2013). The mammalian/mechanistic target of rapamycin (mTOR) complex 1, which serves as both a metabolic sensor and regulator, is recurrently activated in cancers via constitutive activation of growth factor/PI3K/AKT signaling pathways via activating mutations or loss of inhibitors such as PTEN, LKB1, or tuberous sclerosis complex proteins (Laplante and Sabatini 2012; Willems et al. 2012; Fresno Vara et al. 2004; Rodon et al. 2013; Atlas 2012a, b; Song et al. 2012; Sanchez-Cespedes 2011; Luo et al. 2010). Common KRAS mutations have been reported to activate glucose, glutamine, and nucleotide metabolism (Son et al. 2013; Gaglio et al. 2011; Ying et al. 2012). However, the oncogene that has perhaps the best studied role in metabolism is MYC (Dang 2012). Expression of MYC induces profound metabolic reprogramming in cancer, controlling glucose, glutamine, nucleotide, lipid, and amino acid metabolism (Fig. 5.3).

5.5.1 MYC, the Warburg Effect, and Mitochondria

Aerobic glycolysis or the Warburg effect relies on increased uptake and retention of glucose and increased glycolysis to convert this glucose to pyruvate and, consequently, to lactate. In cancer cells, MYC controls a transcriptional program to promote the Warburg effect. Glycolysis requires the uptake of glucose into the cell by glucose transporters. MYC can directly upregulate the glucose transporter GLUT1 (Osthus et al. 2000). After uptake by transporters, glucose is phosphorylated by hexokinases and becomes trapped in the cell. Hexokinase II has been shown to be overexpressed in cancer and can be induced by MYC (Kim et al. 2004). MYC also shows almost uniform upregulation of glycolytic genes, including phosphoglucose isomerase, phosphofructokinase, glyceraldehyde-3-phosphate dehydrogenase, phosphoglycerate kinase, and enolase, binding to the promoters of these genes in upregulating them (Osthus et al. 2000; Kim et al. 2004). By upregulating almost the entire pathway, MYC is capable of enhancing the Warburg effect.

In certain experimental systems, MYC can induce the expression of PKM2 as well as influencing the splicing of the PKM transcript to PKM2 by upregulating the RNA binding splicing proteins HNRNPA1 and HNRNPA2 (David et al. 2010). PKM2 is an important enzyme in cancer metabolism, which differs from its alternative splice form PKM1 in its ability to promote the Warburg effect, regulate pentose phosphate pathway flux, regulate serine biosynthesis, and bind phosphotyrosines (Ye et al. 2012; Anastasiou et al. 2011; Christofk et al. 2008; Chaneton et al. 2012). Upon phosphorylation by ERK, PKM2 but not PKM1 appears to translocate to the nucleus and phosphorylates H3 tyrosine 11 at the MYC promoter, enhancing MYC expression (Yang et al. 2012).

Aerobic glycolysis requires the glycolytic cofactor NAD^+ for the activity of GAPDH. Cancer cells can regenerate NAD^+ from NADH by converting pyruvate to lactate via the enzyme lactate dehydrogenase. MYC directly upregulates the lactate dehydrogenase A (LDHA), promoting the conversion of pyruvate to lactate (Shim et al. 1997). Inhibiting LDHA genetically or pharmacologically diminishes the growth of MYC-dependent cancer cell lines (Le et al. 2010). The buildup of lactate can be toxic to cells, so cancer cells undergoing aerobic glycolysis need to excrete lactate. MYC upregulates the monocarboxylate transporter 1 (MCT1/SLC16A1), which transports lactate out of the cells. Inhibiting lactate export via MCT1 inhibition can result in cell death in MYC-dependent cells (Doherty et al. 2014).

Mitochondria, being the powerhouses of cellular metabolism, are also affected by MYC. Genes involved in mitochondrial biogenesis are upregulated by MYC in both mammals and *Drosophila* (Orian et al. 2003; O'Connell et al. 2003; Morrish et al. 2003; Wonsey et al. 2002; Li et al. 2005). MYC also targets ferritin, IRP1, IRP2, and transferrin receptor (TFRC1) which are all genes involved in iron metabolism largely involving the mitochondrion (O'Connell et al. 2003; Bowen et al. 2002; Wu et al. 1999; O'Donnell et al. 2006). In addition to iron metabolism, nucleotide synthesis genes are also upregulated by MYC, including carbamoyl

phosphate synthetase, aspartate transcarbamoylase, dihydroorotase (CAD), and ornithine decarboxylase (ODC) (Bello-Fernandez et al. 1993; Miltenberger et al. 1995; Liu et al. 2008). Specifically, DHODH, which is a target of MYC, requires a functional mitochondrial electron transport chain for its catalytic conversion of orotate to dihydroorotate in nucleotide synthesis. Hence many pathways influenced by MYC require the function of mitochondria to support cell growth and metabolism.

Although MYC plays an important role in inducing glycolysis and mitochondrial function, tumor cells are often hypoxic due to the imperfect neo-vasculature found in solid tumors. The hypoxia-inducible factor (HIF1) inhibits pyruvate conversion to acetyl-CoA, by shunting it to lactate via activation of lactate dehydrogenase A (LDHA) and pyruvate dehydrogenase kinase (PDK1) that inhibits pyruvate dehydrogenase (PDH). This activation of LDHA, and suppression of PDH by HIF1, stops glucose from supplying carbons to the TCA cycle (Kim et al. 2006). Surprisingly, glutamine's involvement in the TCA cycle persists under hypoxia (Le et al. 2012).

5.5.2 MYC and Glutamine Metabolism

Glutamine is another major bioenergetic source for tumor cells, especially as a source of nitrogen and carbon for nucleotide and amino acid synthesis. Glutamine is imported to the cells through glutamine transporter (e.g., ASCT2). Glutamine is then converted to glutamate by glutaminase. Glutamate can be further metabolized to α-ketoglutarate (αKG) through glutamine dehydrogenase, glutamine pyruvate transaminase (GPT), or glutamine oxaloacetate transaminase (GOT) to enter TCA cycle and be catabolized by the mitochondria.

Cancer cells are addicted to glutamine, which was documented few decades ago, for the following reasons (Reitzer et al. 1979). First, glutamine helps to feed TCA cycle and results in a truncated TCA cycle, which allows acetyl-CoA from glycolytic pathway to be used for de novo fatty acid synthesis and cholesterol synthesis instead of making citrate with oxaloacetate. Fatty acids and cholesterols are important for building new cell membrane. Other intermediates of TCA cycle can also be used for biosynthesis under the constant supply of αKG from glutamine. The role of glutamine to replenish the intermediates in TCA cycle is far more critical in cancer cells than normal cells due to increased biosynthesis. Second, glutamine and its derivatives glutamate and aspartate are source for nucleotide synthesis, which is also increased in proliferated cancer cells.

MYC drives glutamine metabolism by targeting a number of genes that are involved in the pathway. For instance, MYC directly binds to the promoter region of two high-affinity glutamine importers ASCT2 and SN2 and upregulated their mRNA expression to increase glutamine import (Wise et al. 2008). To also increase flux from glutamine to glutamate, MYC activates glutaminase (GLS) both transcriptionally and posttranscriptionally (Wise et al. 2008; Gao et al. 2009). In both

P493 Burkitt's lymphoma and PC3 prostate cancer cell line, MYC activation increases GLS protein at a much higher level compared to mRNA expression, suggesting that MYC regulates mitochondrial GLS indirectly (Gao et al. 2009). Further investigation showed that MYC suppresses miR-23a and miR-23b, resulting in a derepressed GLS protein translation from miR-23a/b (Gao et al. 2009). As a result, elevated GLS facilitates glutamine to enter TCA cycle in the mitochondria.

MYC-overexpressed cells often exhibit addiction to glutamine. High level of MYC appears to prime fibroblast to a glutamine-dependent state (Yuneva et al. 2007). Upon glutamine deprivation, cells underwent apoptosis. This observation, however, can be rescued by oxaloacetate and pyruvate, suggesting TCA cycle intermediate depletion leads to apoptosis (Yuneva et al. 2007). Similar observations were made in glioma cells. Using small-interference RNA (siRNA) targeting MYC helps glioma cells to develop resistance to glutamine deprivation (Wise et al. 2008).

MYC-dependent glutaminolysis is observed to be a critical alternative energy source pathway in nutrient-limiting environment, specifically under glucose and oxygen deprivation conditions (Le et al. 2012). C^{13}-labeled glutamine was used to track the flux of glutamine metabolism in P493 B cell in the presence and absence of glucose. Interestingly, under glucose-deprived condition, much higher levels of these labeled isotopologues of TCA cycle intermediates, such as fumarate, malate, and aspartate, were found compared to glucose-abundant condition (Le et al. 2012). This observation suggests that while glucose is still a preferable carbon source of TCA cycle, glutamine can virtually replace glucose in the absence of glucose. Nevertheless, under glucose-abundant condition, glutamine is used for glutathione synthesis to reduce oxidative stress (Le et al. 2012). Flux analysis using C^{13}, N^{15} glutamine as a tracer in another study has documented that glutamine can also contribute to proline biosynthesis (Liu et al. 2012). A recent study using hyperpolarized C^{13}-pyruvate magnetic resonance spectroscopic imaging (MRSI) to visualize tumor formation and regression in an *MYC*-inducible mouse hepatocellular carcinoma cancer model has observed that glutamine is converted to αKG through increased flux from pyruvate to alanine in premalignant stage (Hu et al. 2011).

A tissue-specific relationship and MYC and glutamine metabolism have been demonstrated in *MYC*-driven liver cancer versus lung cancer (Yuneva et al. 2012). Differential expression of glutamine synthetase determines the direction of glutamine metabolism (Yuneva et al. 2012). For instance, with low glutamine synthetase expression, *MYC*-induced liver tumors exhibit increased glutamine catabolism (Yuneva et al. 2012). In contrast, glutamine accumulation found in *MYC*-induced lung cancers is possibly associated with elevated glutamine synthetase (Yuneva et al. 2012). As tissue origins of tumors can dictate the expression of metabolic pathways, the fate of glutamine can be varied based on the tissue of origin even on the same oncogenic background.

Given that *MYC*-induced tumors rely on glutamine metabolism for cell growth and survival, targeting glutaminase appears to be a feasible way to treat *MYC*-overexpressed cancer. In fact, BPTES, a glutaminase inhibitor, has been shown to

effectively slow down tumor growth in P493 B cells as well as *MYC*-induced tumor xenografts (Le et al. 2012; Wang et al. 2010).

5.5.3 MYC and Amino Acid Transporters and Synthesis

MYC plays a key role in the acquisition and uptake of the amino acids required for cell growth. MYC stimulates the uptake and catabolism of glutamine by upregulating glutamine transporters and the enyzme glutaminase. As discussed above, MYC can drive the synthesis of serine and glycine from glucose via upregulation of key enzymes. Additionally, MYC-driven increase in glutamine metabolism can promote the synthesis of alanine and aspartate, as glutamine-derived glutamate is used to transaminate pyruvate to produce alanine and oxaloacetate to produce aspartate. MYC also promotes the synthesis of proline from glutamine by upregulating proline synthesis genes and indirectly downregulating genes that degrade proline (Liu et al. 2012).

Leucine plays a key role in cancer metabolism through its key role in the regulation of mTORC1 activity (Nicklin et al. 2009). Glutamine can be exchanged through the L-type amino acid transporter (LAT1 composed of SLC7A5 and SLC3A2) for leucine, with glutamine uptake being the rate-limiting step (Nicklin et al. 2009). MYC promote the uptake of glutamine through the regulation of SLC1A5 and then stimulate its exchange for leucine by upregulating SLC7A5 (Gao et al. 2009; Hayashi et al. 2012). While MYC activation has been shown to stimulate leucine uptake (Murphy et al. 2013), the crosstalk between SLC1A5, SLC7A5, MYC, and mTOR remains to be fully elucidated (Sinclair et al. 2013).

5.5.4 Fatty Acid Metabolism

Glucose first enters the cell via glucose transporters and is retained intracellularly once it is phosphorylated by hexokinases. This six-carbon phosphate then is phosphorylated again and split into two three-carbon structures that can then be converted to glycerol. This glycerol can either be used for lipogenesis or to make pyruvate. In the case of its transformation to pyruvate (the process of glycolysis), the pyruvate is then transaminated to alanine with glutamate derived from glutamine as the nitrogen donor or converted to acetyl-CoA in the Krebs cycle. Acetyl-CoA is then transformed into citrate and oxaloacetate, completing the Krebs cycle, generating ATP, carbon dioxide, and other carbon substrates for other pathways. For example, citrate could be exported into the cytoplasm and converted to acetyl-CoA by ATP citrate lyase (ACLY) for lipogenesis.

The pathway for fatty acid synthesis takes place in the cytoplasm. Citrate from the Krebs cycle in mitochondria is first released into the cytoplasm and converted into acetyl-CoA by ATP citrate lyase (ACLY). The production of malonyl-CoA by

acetyl-CoA carboxylase (ACACA) is the first committed step of fatty acid synthesis. Acetyl-CoA carboxylase (ACACA) is the major site of regulation of fatty acid synthesis. Fatty acid synthase (FASN) then converts the malonyl-CoA into a 16-carbon palmitate. Tracing glucose in MYC-induced cells has been shown to be incorporated into increased acetyl-CoA production and in turn increased palmitate synthesis, consistent with the metabolic pathway of glucose conversion to acetyl-CoA and then in turn to palmitate (Morrish et al. 2010). Though this shows the involvement of MYC in lipid metabolism, this also has epigenetic implications, because the traced acetyl-CoA is shown to be incorporated into the acetylation of H4K16.

This upregulation of the lipogenesis pathway by MYC was found in Burkitt's lymphoma, hepatocellular carcinoma, and osteocarcinoma cell lines. However, not all cancers induce lipogenesis. Many prostate cancers oxidize lipids to make ATP (Tennakoon et al. 2013). Others have also shown that pharmaceutical inhibition of lipid oxidation in N-*MYC*-amplified neuroblastoma cells leads to cell cycle arrest, apoptosis, and neuronal differentiation (Zirath et al. 2013). This differentiation is accompanied with lipid accumulation. Gene expression analysis shows inhibition of MYC's correlation with decreased expression of oxidative phosphorylation and fatty acid oxidation genes (Zirath et al. 2013). These observations suggest that cancer metabolic networks depend on the specific cell type, the driving oncogene (s), and the tumor microenvironment.

5.5.5 MYC and Nucleotide Biosynthesis

MYC drives glucose and glutamine metabolism to provide carbon sources for biosynthesis and continually generate ATP to support tumor cell growth and survival. However, for cancer cells to proliferate (increase cell numbers), sufficient supply of nucleotides is equally crucial. Global mapping of MYC target genes using ChIP-PET has indicated that many genes that are involved in nucleotide synthesis pathway are direct MYC targets (Zeller et al. 2006). For instance, the enzymes that are involved in dNTP metabolism, such as inosine monophosphate dehydrogenase (IMPDH), thymidylate synthase (TS), and phosphoribosyl pyrophosphate synthetase 2 (PRPS2), were found to be induced by MYC (Mannava et al. 2008; Liu et al. 2008). Targeting IMPDH by its specific inhibitor mycophenolic acid (MPA) results in apoptosis and S phase arrest in P493 B cells, which can be rescued by exogenous guanosine (Liu et al. 2008).

Despite direct regulation of nucleotide synthesis pathway, MYC also promotes the channeling of glycolytic intermediates to make amino acids that are required for nucleotide synthesis, such as serine and glycine (Vazquez et al. 2011). Glycolytic intermediate 3-phosphoglycerate is oxidized by phosphoglycerate dehydrogenase (PHGDH) and then converted to serine in a series of reactions that are catalyzed by phosphoserine aminotransferase 1 (PSAT1) and phosphoserine phosphatase (PSPH). Further, serine hydroxymethyltransferase (SHMT) can convert serine to

glycine while simultaneously converting tetrahydrofolate to 5,10 methylenetetrahydrofolate. Several studies have shown PHGDH, and PSPH can be induced by MYC (Vazquez et al. 2011). In addition, both mitochondrial and cytoplasmic SHMTs that were documented are direct MYC targets (Nikiforov et al. 2002). However, decreased tumor burden was not found when breed Burkitt's lymphoma mouse model expresses human MYC transgenes with inactivated alleles of PHGDH or SHMT, suggesting that target genes that are involved in serine and glycine pathway individually may not be sufficient (Nilsson et al. 2012).

5.5.6 MYC and Oncometabolites

While altered metabolism in cancers is often thought of as downstream of oncogenes, recent studies have shown that metabolites themselves can contribute to tumor formation most likely through alterations in the cancer epigenome. Mutations in TCA cycle enzymes can lead to the accumulation of succinate and fumarate, which are believed to promote cancer through alteration of epigenetic state and reactive oxygen species (Letouze et al. 2013; Sullivan et al. 2013). As MYC can increase the amount of glutamine entering the TCA cycle, it is possible that the MYC activation could stimulate succinate and fumarate accumulation in the TCA cycle mutant cell lines.

The most studied oncometabolite to date is 2-hydroxyglutarate. Isocitrate dehydrogenase (IDH) catalyzes the formation of alpha-ketoglutarate from isocitrate in the TCA cycle. Mutants IDH1 and IDH2, which are recurrently mutated in several types of cancer including leukemia and gliomas, produce 2-hydroxyglutarate. 2-Hyrdroxyglutarate can inhibit alpha-ketoglutarate-dependent histone demethylases (Chowdhury et al. 2011; Lu et al. 2012) and DNA demethylase Tet2, causing epigenetic changes which inhibit cellular differentiation (Figueroa et al. 2010). However, recent studies suggest that mutant IDH is not the only source of 2-hydroxyglutarate in cancer. A recent study showed the accumulation of 2-hydroxyglutarate in triple negative breast cancers lacking an IDH mutation (Terunuma et al. 2014). These high 2-hydroxyglutarate breast cancers, which exhibited a hypermethylation, showed strong overexpression of MYC and had an MYC expression signature. Knockdown of MYC in these breast cancer cell lines decreased levels of 2-hydroxyglutarate. MYC increased the metabolism of glutamine, which was the source of carbons used to produce the 2-hydroxyglutatarate. While this study suggests that MYC may upregulate 2-hydroxyglutarate, it is not yet known whether this applies to tissues beyond breast cancer.

5.6 MYC-Driven Metabolism and Cancer Therapy

Although MYC is an intriguing therapeutic target, for example, via bromodomain inhibitors, its downstream transcriptional targets and altered metabolism offer additional therapeutic opportunities (Loven et al. 2013; Delmore et al. 2011). Increased understanding of the reliance of cancer on altered metabolism and the mutations that underlie metabolic reprogramming have driven interest in using anti-metabolism therapies to treat cancer. However, once these therapies reach the clinic, it will be challenging to predict which tumors respond to which therapies. Although MYC status will likely not be sufficient to predict therapeutic response to antimetabolic therapies in all cases due to tissue- and tumor-specific effects, MYC-driven metabolic reprogramming provides intriguing therapeutic targets. MYC drives nucleotide metabolism, which is the target of some of the oldest and most successful chemotherapies. Blocking glucose metabolism by inhibiting glucose uptake and glycolysis is challenging due to the reliance of the vast majority of non-cancer cells on glucose. Targeting aerobic glycolysis through inhibition of lactate dehydrogenase or monocarboxylate transporter-dependent lactate export is a potentially viable target; the lack of high-quality inhibitors and the dependence of rapidly growing non-cancer cells on aerobic glycolysis present challenges in targeting aerobic glycolysis (Doherty et al. 2014; Le et al. 2010). Glutamine metabolism was first tried in the clinic using nonspecific amino acid analogues which alter the activity of a large variety of enzymes, leading to off-target effect of lack of efficacy (Rajagopalan and DeBerardinis 2011; Shapiro et al. 1979). However, the identification of allosteric inhibitors of glutaminase have opened the door to a less toxic inhibition of glutamine metabolism (Robinson et al. 2007; Le et al. 2012). A glutaminase inhibitor began clinical trials in early 2014 (Gross et al. 2014).

Conclusion

MYC has been studied over the years as a master oncogenic regulator, especially because it regulates many genes that are crucial for cancer cell growth and proliferation. Among many of its activities, three major functions of MYC were discussed: cell cycle, protein synthesis, and metabolism. In concert with MYC's ability to induce cell proliferation, MYC also upregulates many cellular metabolic pathways that are involved in nutrient import and macromolecular biosynthesis. In essence, MYC is an amplifier of gene expression that coordinates the import of nutrients and the bioenergetics demands of replicating a cell, shunting nutrients into cell biomass. Glucose, glutamine, and lipid metabolic pathways are regulated by MYC in various cells to support the increased demand for energy and raw building blocks of proliferating cells. Normal proliferating cells depend on similar metabolic pathways; however, normal *MYC* expression is dependent on external cues

(continued)

and growth factors, such that altered metabolism induced by MYC is dependent on these external cues. Normal *MYC* expression is attenuated by the absence of growth factors or nutrients. By contrast, cancer cells with deregulated *MYC* expression that no longer requires external cues are forced to undergo cell growth independent of nutrient sensing. In this regard, MYC-dependent cancer cells are addicted to nutrients, such as glucose and glutamine. Insights into these metabolic pathways and how MYC regulates them allow for the identification of new therapeutic targets and provide the hope that new therapies might emerge in the clinic for different types of cancers.

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