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MYC, Metabolism, and Cancer

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Summary

The *MYC* oncogene encodes a transcription factor, MYC, whose broad effects make its precise oncogenic role enigmatically elusive. The evidence to date suggests that MYC triggers selective gene expression amplification to promote cell growth and proliferation. Through its targets, MYC coordinates nutrient acquisition to produce ATP and key cellular building blocks that increase cell mass and trigger DNA replication and cell division. In cancer, genetic and epigenetic derangements silence checkpoints and unleash MYC's cell growth- and proliferation-promoting metabolic activities. Unbridled growth in response to deregulated MYC expression creates dependence on MYC-driven metabolic pathways, such that reliance on specific metabolic enzymes provides novel targets for cancer therapy.

MYC function

c-MYC (termed MYC henceforth), like its family members N-MYC and L-MYC, is a transcription factor that dimerizes with MAX to bind DNA and regulate gene expression (1). A nuclear localization sequence, DNA binding domain, helix-loop-helix (HLH) dimerization domain, and transcriptional regulatory domain underlie this functional ability. MYC was first discovered as the cellular homolog of the retroviral *v-myc* oncogene identified from studies of oncogenic retroviruses (2–4). Soon after its discovery, chromosomal translocations that juxtapose *MYC* to immunoglobulin enhancers were documented in B cell Burkitt lymphomas (5). Classical *in vitro* assays using normal primary rat embryo fibroblasts then documented *MYC*'s transforming activity in cooperation with activated RAS and the sufficiency of these two oncogenes to transform normal cells (6). Tightly regulated in non-cancerous cells (Figure 1A), *MYC* is now known to be one of the most frequently deregulated oncogenes. It is frequently translocated in hematopoietic cancers and was found in a pan-cancer copy number analysis to be the third most amplified gene in human cancers (Figure 1B) (7, 8). Deregulated expression of MYC in transgenic murine tissues of many varieties can trigger tumorigenesis in those tissues, illustrating its transforming activity *in vivo* and supporting the notion that it is a human oncogene (9).

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Conflicts of Interest

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Because of its oncogenic potential, the *MYC* proto-oncogene is tightly regulated in normal cells at the transcriptional and post-transcriptional levels (Figure 1A) (10). Post-transcriptionally, it is regulated by microRNAs and by translation of its mRNA (11–13). Post-translationally, Myc protein half-life and transcriptional activity are controlled by kinases, ubiquitin ligases, acetyl transferases and other interacting proteins (11–16), and indeed, oncogenic KRAS and ERK can upregulate Myc in part through enhanced protein stability (17–20). Recent studies show that long non-coding RNAs control MYC activity and protein stability altering post-translational modification (15, 21). Exquisite regulatory restraint is also achieved through the governance of *MYC* proto-oncogene enhancers that appear cell-type specific (22–25) (Figure 2A). Many growth-promoting signal transduction pathways downstream of ligand-membrane receptor engagement, such as Notch and EGFR converge on *MYC*, underscoring the centrality of MYC to cell growth regulation (26–32) (Figure 2A). Activation of the proto-oncogene is invariably dependent upon such stimulation by growth factors. In contrast, in cancer, *MYC* amplifications that increase *MYC* copy number, translocations that pair *MYC* with highly active enhancers, or viral insertional events in the *MYC* locus sever MYC from its dependence on growth factor signaling (1) (Figure 1B and 2B). Changes in the activity of *MYC*'s enhancers can likewise uncouple MYC expression from its normally required stimuli, affecting cancer risk and progression. For example, Notch-dependent enhancers of *MYC* appear to be intimately involved in activation of *MYC* in human T-cell lymphoma (22, 23). Other enhancers exhibit single nucleotide polymorphisms that affect transcriptional activator TCF-7 binding and predispose to prostate and colon cancer (33–36).

In non-cancerous cells, check-points further protect against deregulated MYC expression. As such, in experimental transgenic models, acute deregulated *MYC* expression does not induce cell proliferation; rather, it results in the activation of checkpoints including those through p53, ARF, BIM, and PTEN that can cause cell growth arrest or death (Figure 2A) (37–40). For example, in a MYC driven lymphoma model increased nuclear localization of the transcription factor FOXO3a can activate ARF to suppress growth (41). Further, ARF can bind MYC and directly inhibit its transcriptional activity (42). Loss of these checkpoints synergizes with MYC to promote transformation. Not surprisingly then, AKT, which can phosphorylate and inhibit FOXO3a, cooperates with MYC in neoplastic transformation (43). Genetic inactivation of FOXO3a can substitute for AKT activation and was documented to be sufficient to transform primary murine embryonic fibroblasts in cooperation with MYC (43) (Figure 2A). These observations are consistent with the finding that MYC-driven murine lymphomas are all virtually devoid of p53 or ARF, indicating that elimination of checkpoints are essential for MYC-mediated tumorigenesis (38). Indeed, human Burkitt's lymphoma loses TP53 in up to 40% of cases (44, 45).

The MYC-MAX heterodimeric transcription factor has been documented to bind consensus DNA sites, termed E-boxes (5′-CACGTG-3′), with high affinity and non-consensus sites with lower affinities (Figure 2) (46). MYC binding to proximal gene promoter sequences relieves transcriptionally paused RNA polymerases and catalyzes transcriptional elongation (Figure 3A) (47). In this regard, it has been proposed that MYC is a general transcription factor which amplifies the expression of genes that are already expressed at basal level,

seemingly without any specificity (“general amplification” model) (48–50). The general amplification model, however, does not account for the ability of MYC to repress genes, such as those activated by the transcription factor MIZ-1 (46). Thus, counter to this general amplifier viewpoint is the hypothesis that MYC targets are largely dictated by chromatin accessibility (51), which permits MYC to bind target genes and cooperate with other transcription factors to activate or repress gene expression selectively (“selective amplification”) (52, 53). That is, the degree by which MYC stimulates expression of a gene is dependent on other transcription factors bound to the gene and or to nearby enhancers.

Two recent papers provide evidence of both selective gene expression amplification that promotes cell growth and direct gene repression by MYC (53, 54). As non-dividing cells tightly control their expression of metabolic enzymes to tailor metabolism for homeostasis, it stands to reason that MYC activation would selectively amplify many metabolic genes required for the building blocks required for growth. Genes involved in non-proliferative cellular functions and cell cycle inhibition driven by MIZ-1 would, on the other hand, be repressed by MYC (54). Collectively, the studies suggest that MYC binds DNA to promote gene expression by relieving paused RNA polymerases. However, the means by which MYC binds DNA and activates or represses gene expression is influenced by chromatin accessibility that is marked by factors such as WDR5, which was recently shown to be required for MYC to bind its targets (55). Indeed, recent work suggests a centrally degenerate E-box motif in closed chromatin may be accessible to MYC employing a partially unfolded DNA-binding domain when assisted by other factors, adding a structural rationale to the idea that MYC’s ability to impact gene expression is a confluence of DNA consensus sequence affinity, chromatin accessibility, and interaction with other proteins (56). Overexpression of MYC can in turn upregulate chromatin modifiers to further alter chromatin accessibility, as suggested by the MYC mediated induction of the Polycomb complex member EZH2 (40, 57, 58). In addition, high levels of deregulated oncogenic MYC further perturb transcription by invading enhancer sequences, causing non-linear amplification of target gene expression and supporting constitutive biomass accumulation in cancer cells, which are driven by MYC (48, 53, 54). However, it is notable that high levels of MYC did not further increase biomass in U2OS cells, but instead induced genes involved in processes such as angiogenesis, metastasis and cell migration (54). U2OS cells are distinct, however, because ectopic MYC expression is detrimental, resulting in cell death rather than promoting cell growth and proliferation (48, 53, 54) (Figure 2B). Regardless of the exact function of MYC in regulating gene expression, studies to date support the notion that activation of MYC results in a genomic program that promotes ribosome biogenesis, cell growth and subsequently cell proliferation (8, 59).

In addition to its transcriptional role, MYC has roles both indirect and direct (i.e. independent of transcription) in regulating protein translation (Figure 3B). As will be discussed further in later sections, MYC transactivates genes encoding the RNA and protein components of ribosomes as well as the nutrient importers and nucleotide synthesis enzymes needed to support this ribosomal assembly. Additionally, MYC promotes cap-dependent translation through the direct stimulation of cap methylation and the transcriptional activation of translation initiation factors and genes involved in mRNA capping (60–66).

The production of tRNAs is also stimulated through MYC's effects on Pol III transcription (67).

Building a cell

T cell lymphocytes serve as a useful model for understanding the role of the transcriptional program driven by growth factor-regulated (non-cancerous) MYC in normal cells (68). Resting, non-proliferating cells, such as dormant stem cells or memory T cells, need nutrients for homeostasis. Maintenance of cell membrane potentials and protein synthesis are two major energy demanding cellular processes that must be sustained for survival (69). Energy and nutrients are also required during homeostasis for redox control and replacement of damaged macromolecules and organelles (70, 71). Intriguingly, in the case of resting memory T cells, a major source of energy for homeostasis is a futile cycle of oxidation of *de novo* synthesized lipids (72). Glucose and glutamine carbons are imported into cells and then converted to citrate for lipogenesis. In contrast to MYC-mediated proliferating cells, which use *de novo* lipogenesis to produce membranes for cell growth, resting T cells oxidize the *de novo* synthesized fatty acids for ATP production. Additional studies to determine whether dormant cancer cells use this previously unsuspected memory T cell futile cycle may reveal additional metabolic rewiring pathways used by cancer cells (73, 74).

Upon experimental growth stimulation with anti-CD3 and anti-CD8 antibodies, normal T cells are activated through the T-cell receptor, which transmits growth signals that induce metabolic changes required for proliferation. T cells from mice with floxed alleles of *Myc* have revealed that the transcriptionally driven metabolic reprogramming necessary for T cell proliferation requires *Myc* (68). Elimination of floxed *Myc* by Cre recombinase resulted in T cells that were unable to mount a growth response. This study corroborates previous studies documenting the role of MYC in driving a transcriptional program that promotes cell metabolism, growth, and proliferation, as will be discussed in detail in subsequent sections (68). Once stimulated, T cells begin to acquire nutrients, particularly glucose and glutamine, and convert them to the necessary components for making new DNA and RNA, new enzymes, new cytoskeleton, new membranes, new organelles, and new copies of genetic material (Figure 4). Ribosomes, which mediate translation of existing mRNAs in the resting cell for homeostasis, become especially critical during cell growth. Once a requisite cell size is reached and adequate nucleotide pools are achieved, the cell undergoes DNA replication while constantly monitoring the replicated DNA for errors and correcting them. After DNA is replicated, the cell then undergoes division using components, such as the cytoskeleton and membrane components, built from the raw nutrients that were required to overcome the checkpoints blocking cell cycle progression.

Nutrient sensing, FOXO, HIF, and MYC

The availability of nutrients is essential for cell growth and proliferation. In fact, lower organisms have developed nutrient sensing mechanisms that are coordinated with growth. The yeast *Saccharomyces cerevisiae* has a remarkable glucose and glutamine sensing mechanism that involves signaling through Target of Rapamycin Complex (TORC) to inhibit two key transcriptional repressors of ribosome biogenesis, Dot6 and Tod6 (75).

Nutrient insufficiency causes decreased TORC signaling, resulting in the inhibition of the production of ribosomes and cell growth through the activation of Dot6 and Tod6 (75). Yeast mutants lacking these functional repressors are rendered constitutive for cell growth, causing them to be 'addicted' to nutrients, such that withdrawal of glucose and glutamine culminates in non-viability. With nitrogen starvation in the presence of limited carbon sources, normal yeast cells undergo meiosis and sporulation that suspends yeast cells in a quiescent metabolic state (76). The slime mold *Dictyostelium discoideum* are amoeba-like unicellular organisms that have a life cycle of active feeding on bacteria. When nutrients become scarce, *Dictyostelium* aggregate to form a slug and then a fruiting body for sporulation in a TOR dependent manner (77, 78). The released spores can be re-animated into amoebae when nutrients become available again. These TOR regulated adaptive mechanisms are recapitulated in the higher organism *Caenorhabditis elegans* which can go into the dormant 'dauer' state with severe nutrient deprivation (79, 80). Hence, throughout evolution, organisms incorporate adaptive mechanisms in response to periods of feast and long periods of famine (81).

However, mammalian cells, owing to perfusion by the circulatory system, are constantly bathed in nutrients, particularly when food and oxygen are available. Under starvation a number of adaptive mechanisms have evolved that are cell intrinsic as well as non-cell autonomous (82). At the organismal level, fat depots and the liver are two major energy storage sources. White fat can be mobilized by lipolysis in response to starvation, while liver glycogen, synthesized from excess glucose, can be mobilized through glycogenolysis. While poorly vascularized tumors or acutely ischemic tissues may have disruption of nutrient availability, these organismal level processes and others normally maintain sufficient circulating levels of key nutrient sources, including a tightly regulated glucose level and more dynamic levels of circulating lipoprotein particles and glutamine, the most abundant plasma amino acid (83). With severe starvation or pathologic processes that disrupt tissue perfusion, cell autonomous nutrient-sensing mechanisms protect cells through pathways aimed at preserving adequate ATP pools. The mammalian Target of Rapamycin (mTOR), AMP kinase (AMPK), and GCN2 pathways are key to survival of cells under nutrient deprivation. Lack of amino acids attenuates mTOR activity through sensing by the Rag proteins on the lysosomal membrane (84), thereby both diminishes protein synthesis and cellular processes that would consume nutrients and ATP and relieves the inhibitory block on autophagy (84). Deprivation of amino acids also results in non-aminoacylated tRNAs that bind to and activate GCN2 and the stress response transcription factor ATF4, which mediates the unfolded protein response (85). When ATP is consumed and AMP is produced, AMPK is activated and its phosphorylation of key substrates(86), such as acetyl-CoA carboxylase (ACACA), diminishes fatty acid synthesis and other high energy consuming pathways. AMPK also increases glycolysis and activates autophagy to produce ATP while simultaneously inhibiting mTOR to slow energetically costly macromolecule synthesis (86).

In addition to its response to growth factor stimulation, MYC also appears to be involved in nutrient sensing downstream of different signaling pathways. As discussed, the yeast *Saccharomyces* cerevisiae senses glucose and glutamine to regulate ribosome biogenesis and cell growth (75). While yeasts do not have a MYC homolog, *Drosophila dMyc* is

functionally equivalent to mammalian MYC. Intriguingly, with nutrient starvation, diminished TOR activity attenuates cell growth through diminished expression of *dMyc*. This pathway appears to involve TOR-dependent AKT phosphorylation and inactivation of FOXO transcription factors, which bind to and negatively regulate *dMyc* expression through a FOXO-responsive cis-element that senses nutrients through TOR and FOXO (87). Mutation of the *dMyc* FOXO-responsive cis-elements renders the mutant flies nonviable with nutrient depletion. Mammalian MYC activity also depends on nutrient status sensed through mTOR via mTOR's regulation of MYC translation (Figure 2A) (14, 88). Further, PI3K/AKT inhibits mammalian FOXO, which when active antagonizes MYC through several mechanisms (89). FOXO3a can transactivate the MYC antagonist and transcriptional repressor, MXI-1 (also called MXD2), which dimerizes with MAX to bind and inhibit MYC target genes (90). Additionally, FOXO3a was documented to inhibit mitochondrial biogenesis by antagonizing MYC's ability to activate genes involved in mitochondrial function (91, 92). Downstream of the mTOR complex 2 or MK5/PRAK, FOXO3a activity can also control MYC levels through induction of miR-34b/c (93, 94). Additionally, mTOR-dependent nutrient sensing controls MYC stability through the autophagy scaffolding protein AMBRA1 (95). When mTOR is inhibited by branched amino acid starvation, AMBRA1 promotes dephosphorylation of serine 62 of MYC by protein phosphatase 2 (PP2A). This dephosphorylation, which destabilizes MYC, is rescued by AMBRA1 downregulation (95). These studies collectively indicate that nutrient sufficiency and growth factor signaling are required for MYC to carry out its transcriptional program—a transcriptional program that serves to propagate the translational growth program triggered by mTOR, a key activator of cap-dependent translation (96).

In addition to nutrients, oxygen is also required for various metabolic enzymatic activities and for proper mitochondrial function. As such, limitation of oxygen, termed hypoxia, also regulates MYC function. In non-transformed cells, endogenous MYC function can be attenuated by hypoxia at several levels including protein stability and protein function. Under hypoxia, MYC protein levels are diminished by proteolytic degradation that can be accentuated by concurrent glucose deprivation (97, 98). Through substrate (O_2) limitation, hypoxia diminishes hydroxylation of HIF-α subunits by prolyl hydroxylases (PHDs), which would otherwise lead to targeting of HIF-α subunits for rapid proteasomal degradation (99–101). Additionally, hypoxia-induced reactive oxygen species can contribute to the stabilization of HIF-1α (102). HIF-1α is pivotal for hypoxic survival through its transcriptional activation of target genes involved in glycolysis and attenuation of mitochondrial function. HIF-1α activates the expression of MXI-1, a MYC antagonist that attenuates MYC induced mitochondrial biogenesis (98, 103). Another study suggests that HIF-1α can compete directly with MYC by binding MAX (104). The complexity of the crosstalk between HIF and MYC is further heightened by the role of the HIF-1α target FOXO3a, which antagonizes MYC in a multitude of ways as discussed above (91, 92). As an attenuator of ROS (91), hypoxia-induced FOXO3a could reduce HIF-α stabilization, reminiscent of the negative feedback loop in which HIF-mediated activation of prolyl hydroxylases in turn decreases HIF-1α protein levels (105). Interestingly, however, overexpressed MYC can both overwhelm ROS-attenuating mechanisms induced by FOXO and bypass the repressive activity of HIF on MYC. HIF-1α and MYC, hence, can cooperate

when MYC is overexpressed (106). By contrast, HIF-2α has been reported to promote MYC-MAX activity and therefore cooperates presumably with both endogenous and ectopic MYC (104). Nutrient and hypoxia sensing in non-transformed cells, therefore, are not equivalent to the rewiring of nutrient sensing and metabolism in MYC-transformed cells, which have lost many of the feedback regulatory loops that restrain cell growth under nutrient or oxygen deprivation.

MYC, intermediary metabolism, and macromolecular synthesis

Despite different levels, endogenous and oncogenic MYC appear to share target genes involved in several facets of intermediary metabolism from glycolysis and glutaminolysis to nucleotide and lipid synthesis (46). In this regard, we surmise that the posited gene expression amplifier function of MYC is compatible with MYC's ability to alter metabolism across many cell types, particularly since nearly all cells basally express metabolic genes, such as those encoding enzymes required for glycolysis, mitochondrial function, and oxidative phosphorylation. When MYC is induced, metabolic genes that are already expressed would be further amplified to support the bioenergetic needs of the growing cell (46). In fact, many canonical MYC target genes involved in metabolism have conserved high affinity MYC consensus E-box binding sites in their proximal promoters (53, 107). Non-consensus sites to which MYC binds with lower affinities, particularly when MYC levels are high and deregulated, have also been identified (Figure 2B)(48). In addition to the presence of other transcription factors, the binding of MYC to any gene locus is dictated by open chromatin structure as well as the binding site affinity (53). Hence, it is hypothesized that MYC would occupy the highest affinity binding sites at lower levels of MYC (46). In retrospect, it does not seem surprising now that some of the earliest MYC-responsive genes identified are involved in metabolism, such as lactate dehydrogenase A (LDHA) and ornithine decarboxylase (ODC), enzymes involved in glycolysis and polyamine synthesis (108, 109). Both of these genes have canonical MYC E-boxes in their proximal promoter regions. As the low throughput candidate gene or subtraction cloning approaches are replaced by unbiased genome-wide gene expression and chromatin-immunoprecipitation (ChIP) analyses using next-generation sequencing, we now witness the entire spectrum of MYC's transcriptional perturbation across the genome and its encoded metabolic pathways (48, 50, 53).

Glycolysis and Glutaminolysis

Cancer cells show profound metabolic changes that provide the energy and building blocks to sustain proliferation (Figure 4). The first noted change in cancer metabolism was the increased conversion of glucose to lactate discovered by Otto Warburg over 90 years ago (110, 111). Later studies indicated that glutamine, the most abundant circulating free amino acid in human plasma, can act as a source of carbon and nitrogen in cancer cells (112). In glutaminolysis, the enzyme glutaminase converts glutamine taken up by the cell to glutamate, which in turn, is converted by glutamate dehydrogenase or transaminases to α-ketoglutarate that is further catabolized in the TCA cycle (Figure 4). Similar to MYC dependent activated lymphocytes (68), MYC-transformed cells were found to have increased glucose and glutamine utilization and increased expression of key glycolytic and

glutaminolytic enzymes (107, 108, 113–116). Previous studies documenting MYC's regulation of glycolytic and glutaminolytic genes are now corroborated by genome-wide RNA-seq and ChIP-seq studies (48). MYC, in essence, regulates virtually all genes involved in glycolysis and many in glutaminolysis (113, 114, 117, 118). It also is particularly notable that MYC appears to not only drive expression of these genes but also favor specific mRNA splice variants, such as glycolysis-impacting PKM2 over PKM1 (119). Although resting cells also express many enzymes in these metabolic pathways, cells that are stimulated to grow must take up nutrients and catabolize these nutrients to make key building blocks. To achieve this end, MYC drives transcription to ultimately generate not only the enzymes that directly constitute these metabolic pathways but also the plasma membrane nutrient transporters needed to supply them. Key MYC targets include glucose membrane transporters such as GLUT1 (or SLC2A1) and glutamine transporter SLC1A5 (or ASCT2) (113, 114), loss of function of which diminishes cell proliferation and highlights their critical importance in cell growth (113, 115). Likewise, knock-down or inhibition of key enzymes in glycolysis or glutaminolysis diminishes cell growth.

MYC-driven buildup of glycolytic intermediates also fuels pathways that share intermediates with glycolysis. The pentose phosphate pathway (PPP), which uses glycolysis-derived glucose-6-phosphate as a starting substrate, produces the reducing equivalent NADPH and the nucleotide synthesis substrate ribose (Figure 4). Through upregulation of enzymes in the pathway, MYC has been shown to increase shunting of glucose to the PPP in both cancer and lymphocytes (68, 120). The glycolytic intermediate 3-phosphoglycerate can be shunted to synthesize serine (Figure 4), which in the mitochondria can be converted to glycine while producing 5,10-methylenetetrahydrofolate (5,10-CH2-THF) by the mitochondrial enzyme serine hydroxymethyltransferase 2 (SHMT2). 5,10-CH2-THF can then be converted to formate by methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), which also generates the reducing equivalent NADPH. Folate plays a key role in nucleotide synthesis and the production of carbon donors that regulate epigenetic marks (121). While the role of MYC in regulating lymphocyte serine biosynthesis is poorly understood (68), serine biosynthesis increased in cancer by MYC through the elevation of the expression enzymes in the pathway (120, 122–125).

As both glucose and glutamine oxidation in the mitochondria generate reactive oxygen species, sufficient levels of the anti-oxidant tripeptide glutathione (L-glutamyl-L-cysteinyl-glycine) or peroxiredoxins (which are induced by MYC (126)), must be maintained to effectively titrate and attenuate these otherwise damaging byproducts. Glutamine-derived glutamate and glucose-derived glycine are themselves substrates for the synthesis of glutathione. Additionally, the NADPH derived from glucose through the PPP and serine metabolism, as well as glutamine-derived NADPH (via malic enzyme (127, 128)), is essential to the regeneration of glutathione, in addition to its role in reductive biosynthesis and redox homeostasis. Indeed, MYC-regulated SHMT2-dependent NADPH production was shown to be required for redox control and cell survival of MYC transformed cells in hypoxia (129). Intriguingly, *SHMT2* was identified as the only gene that could partially rescue the slowed growth of *Myc*-null fibroblasts in an expression screen (130). Additionally, genetic reduction of MTHFD2 leads to oxidative stress, illustrating the

importance of this pathway in a model cell culture system (131). Glucose and glutamine, hence, play a vital role in the production of ATP, reducing equivalents for biosynthesis, and building blocks for growing cells.

Metabolism of glucose and glutamine also produces toxic byproducts and acids that must be eliminated (Figure 4). Lactic acid produced from glucose is extruded by monocarboxylic acid transporters MCT1, a MYC target, and MCT4, a target of HIF-1α (132, 133). Inhibition of either of these transporters can markedly diminish cell growth or *in vivo* tumorigenesis (132, 133). Glutaminolysis involves the production of ammonia, which can be toxic. The mode by which cells eliminate ammonia metabolically is not well understood other than what we know about the urea cycle, which is found in specialized cells. Some cells express glutamine synthetase that can produce glutamine from glutamate and ammonia, while transaminases can deaminate glutamine and glutamate without producing ammonia (134, 135). Additional studies are necessary for fuller understanding of ammonia metabolism in cancer cells.

De novo nucleotide synthesis

The increased nucleotide synthesis required by cancers to maintain proliferation necessitates the coupling of nucleotide synthesis and the reprogramming of metabolism. MYC coordinately regulates nucleotide synthesis enzymes and other metabolic enzymes to achieve this increased nucleotide production (Figure 4). MYC binds to and regulates many genes involved in purine and pyrimidine synthesis (136, 137). Importantly, the generation of glycine from glucose and aspartate from glucose or glutamine are major contributors to the synthesis of purines and pyrimidines, respectively. In purine metabolism, MYC binds to the bi-directional promoter of phosphoribosyl pyrophosphate amidotransferase (*PPAT*) and phosphoribosylaminoimidazole carboxylase, phosphoriboxylaminoimidazole succinocarboxamide synthetase (*PAICS*), but regulates these genes differentially as they serve at different steps in purine synthesis. In pyrimidine synthesis, MYC is known to regulate carbamoyl-phosphate synthetase (*CAD*), one of the earliest identified MYC target genes (138). In addition, MYC directly regulates dihydroorate dehydrogenase (*DHODH*), an enzyme that couples with the mitochondrial electron transport chain to oxidize dihydroorotate to orotic acid, a pyrimidine precursor. In a time-series study of the human P493-6 lymphoma model cell line, these target genes had variable responses to MYC induction with phosphoribosylformylglycinamidine synthase (*PFAS*) in purine synthesis being most highly activated (136). Many of these genes were also induced by MYC *in vivo* using a transgenic model of inducible MYC in mouse liver (136). High-throughput genome-wide ChIP-seq experiments corroborated MYC binding to these genes as documented earlier by ChIP-PCR (48, 139, 140). Knockdown of MYC in various cell lines also resulted in diminished nucleotide gene expression providing the converse evidence for nucleotide metabolic genes as MYC targets. Further, ectopic expression of the MYC targets thymidylate synthetase (*TS*), inosine-5′-monophosphate dehydrogenase (*IMPDH2*), and *PRPS2* diminished the proliferative arrest caused by MYC knock-down, illustrating the functional role of nucleotide biosynthesis in MYC-induced cell growth (137).

In addition to glucose and glutamine, *de novo* synthesis of nucleotides also requires folate as co-factor for various enzymatic steps (121). *De novo* synthesis of purines occurs on the PPP-derived ribose-5-phosphate scaffold, which is derived from glucose. Biochemical activation of ribose to phosphoribose pyrophosphate (PRPP) by the enzyme phosphoribosyl pyrophosphate synthetase (PRPS2) and ATP prepares the scaffold for addition of a nitrogen from glutamine, which initiates the purine scaffold that is sequentially built up with glycine, additional glutamine nitrogens, and single carbons transferred from the folate carrier. MYC coordinates the increase in PPP activity, glycine and folate synthesis and glutamine uptake to fuel nucleotide production.

Nucleotide synthesis was recently linked to MYC-regulated protein synthesis for cell growth (Figure 3B). MYC has been shown to control protein synthesis through its involvement in ribosome biogenesis (detailed below), induction of eukaryotic translation initiation factors—including eukaryotic translation initiation factor eIF4E, an early documented MYC target gene (66, 141)—and its direct promotion of mRNA cap methylation(61). In essence, MYC regulates both ribosomal biosynthesis and components of the cap-dependent translation to control machinery to stimulate mRNA capping and protein synthesis (60, 61, 64–66, 141–145). Haploinsufficiency of the ribosomal protein-encoding *Rpl24* gene was documented to diminish MYC-induced lymphomagenesis in *Eμ-Myc* transgenic mice, demonstrating the critical role of ribosome function and translation for MYC-induced tumorigenesis (146). A recent study found that *Eμ-Myc* mice with normalized translation rates dues to *Rpl24* haploinsufficiency show reduced nucleotide pools in B cells expressing oncogenic MYC. Profiling of protein levels of nucleotide synthesis enzymes found that PRPS2 was unique in that its protein levels were markedly diminished in *Rpl24* haploinsufficient MYC-driven cells. Although *Prps2* is a direct transcriptional target of MYC (137), its translation is intriguingly regulated by a pyrimidine-rich translational element (PRTE) in the 5′ untranslated region of the *Prps2* mRNA, which makes it proportionately sensitive to increased translation rates driven by MYC downstream of eIF4E activation(147). As mentioned, PRPS2 catalyzes a critical step in purine synthesis by converting ribose-5-phosphate to PRPP. Importantly, *Prps2* knockdown is synthetically lethal in MYC-overexpressing cells, such that loss of PRPS2 prolonged the survival of transgenic mice with MYC-induced lymphoma. These studies illustrate that MYC-overexpressing cells are dependent on balanced translation and nucleotide synthesis, which are coupled through the regulation of PRPS2 translation.

Lipid synthesis

Membrane genesis is essential for a growing cell, and, correspondingly, MYC plays a key role in stimulating fatty acid and cholesterol synthesis. In addition to stimulating TCA cycle genes responsible for producing citrate, which is a critical precursor of fatty acids and cholesterol, MYC also activates the expression of the enzymes ATP citrate lyase (ACLY), acetyl-CoA carboxylase alpha (ACACA), fatty acid synthase (FASN), and stearoyl-CoA desaturase (SCD), which are all involved in fatty acid synthesis from citrate (148–150). ACLY converts citrate to acetyl-CoA in the cytosol and ACACA generates malonyl-CoA from acetyl-CoA. FASN catalyzes fatty acid chain elongation from the malonyl scaffold, while SCD monosaturates long chain fatty acids, for example converting palmitate to oleate.

In addition, tracer studies document the role of MYC in driving labeled glucose carbons into fatty acids (149). Because glutamine can contribute to the TCA cycle, lipids also contain carbons derived from glutamine. As discussed above, the production of NADPH by the pentose phosphate, serine biosynthesis, and malic enzyme pathways is crucial to this reductive biosynthetic ability of MYC-driven cells.

Intriguingly, the ability of MYC to induce mitochondrial biogenesis (see below) and function appears to affect lipid metabolism indirectly. With loss of MYC function in knockout fibroblasts or in a neuroblastoma cell model, decreased mitochondrial production is associated with accumulation of lipid vacuoles, indicating that under unique circumstances MYC can stimulate fatty acid oxidation through increased mitochondrial biogenesis (150, 151), implying that MYC may play both anabolic and catabolic roles in lipid metabolism.

MYC, metabolism and organelle biogenesis

As a growth-promoting transcription factor, MYC stimulates metabolic pathways that support formation of new organelles, particularly ribosomes and mitochondria, which in turn is required for ATP generation and the production of many substrates for cell growth (152). The means by which a cell grows largely depends upon sufficient mitochondria, to produced building blocks and energy, and ribosomes to increase genomic output through translation.

Ribosomes

MYC is a unique transcription factor that stimulates transcription driven by all three RNA polymerases (I, II, and III) to produce components of the ribosome: rRNA, ribosomal proteins, and small 5S rRNAs (153, 154). MYC's global ability to amplify gene expression allows MYC to relieve transcriptionally paused genes involved in ribosome biogenesis (142, 155). This role of MYC in the production of ribosomes is highlighted in *Drosophila*, as a hypomorphic *dMyc* allele causes the *diminutive* mutant fly phenotype (156–158). The small body and cell size associated with the *diminutive* fly phenocopies flies that belong to the large complementation group of small flies termed *Minutes* (159). *Minutes* are largely comprised of flies that have hypomorphic ribosomal protein genes. Thus, *dMyc* is linked to ribosome biogenesis through this group of *Minute* flies.

The links between MYC and ribosomes established in flies are further underscored by the enrichment of canonical MYC E-boxes in the promoters of ribosome biogenesis genes, conserved not only in flies but also down to the unicellular eukaryote, *Nemostella* (160). The connection between MYC and ribosome biogenesis is also recapitulated in mammals. Early studies of the P493-6 inducible-MYC human B lymphoma model cell line demonstrated that MYC could increase cell size independent of cell proliferation (161). MYC was shown by various studies of P493-6 cells to directly induce genes involved in ribosome biogenesis. In addition, acute adenoviral-mediated ectopic expression of MYC in mouse liver resulted in significant hepatocellular hypertrophy within a matter of days associated with highly elevated expression of ribosomal protein genes (162). MYC's role in ribosome biogenesis is further illustrated by a cell-type-independent MYC target gene signature and the association of heightened ribosomal biogenesis in connection with MYC expression in human prostate

cancer (163, 164). These studies collectively illustrate the ability of MYC to stimulate ribosome biogenesis, which is now corroborated by genome-wide studies of MYC target genes (48, 50, 53, 54). Intriguingly, haploinsufficiency of *Myc* prolongs mouse lifespan and is associated with a decrease in ribosome biogenesis (165). As treatment of mice with rapamycin, which inhibits mTORC1, or metformin, which inhibits mitochondrial Complex I activity can also increase lifespan, this study links lowered metabolic demands with longevity and further highlights the role of ribosomes in mediating phenotypic effects of MYC (166–168).

Mitochondria

Mitochondria are essential organelles not only because respiration and oxidative phosphorylation produce ATP, but also because they serve as vital hubs for a number of biosynthetic pathways including nucleotide, fatty acid, cholesterol, amino acid, and heme synthesis (169, 170). Iron is required for mitochondrial function and a key MYC responsive gene is the transferrin receptor, TFRC, which imports iron essential for cell growth (171). Further, mitochondria are important to support transcription, since mitochondrial mass directly influences an overall rate of transcription in a cell (126, 171–174). Thus, as a cell grows, the number of mitochondria must also increase. While factors that control mitochondrial biogenesis for homeostasis have been well-established, the means by which mitochondrial biogenesis occurs in response to cell growth has only more recently been proposed (169). Unlike resting cells, which maintain mitochondrial homeostasis through peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) and peroxisome proliferator-activated receptors (PPARs), proliferating cells appear to be under the control of MYC, which coordinately activates the expression of PGC1β and the mitochondrial DNA polymerase gamma, as well as many components of the mitochondria, for mitochondrial growth or biogenesis (98, 113, 116, 126, 149, 173, 175, 176). Importantly, key components of the mitochondrial machinery that are induced by MYC seem to be vital because knocking down or inhibiting these elements is synthetically lethal in MYC-overexpressing cells (177, 178). In this regard, anti-retroviral agents for treatment of HIV, which can inhibit mitochondrial DNA polymerase gamma, may have activity against MYC-driven tumors (179).

MYC controls many components of intermediary metabolic pathways that are confined to the mitochondrion, thereby affecting mitochondrial function. Enzymes in these pathways include glutaminase (GLS), which converts glutamine to glutamate for use in the TCA cycle. *IMPDH2* and *DHODH* are MYC targets that produce mitochondrial enzymes involved in purine and pyrimidine synthesis (see above). Components of the mitochondrial folate pathways, such as SHMT2 and MTHFD2, are MYC targets along with the vast majority of the TCA cycle enzymes that reside in the mitochondrion. In addition, MYC may also control mitochondrial dynamics, altering the rates of mitochondrial fusion and fission that also influence mitochondrial function (180). Correspondingly, loss of *Myc* function through Cre recombinase treatment of T cells with floxed allele of *Myc* or in knockout fibroblasts was associated with severely deficient mitochondrial mass and morphology (173). A key function of MYC, therefore, is the coordination of cell and mitochondrial growth, which is potentially exploitable for therapy.

Other organelles

Much less is understood about how MYC influences the generation or maintenance of other organelles, but it appears that MYC does not increase the genesis of all organelles. In particular, it appears that MYC suppresses lysosomal biogenesis and autophagy in several experimental systems. MYC can antagonize MIZ-1 functions, which include the maintenance of autophagic flux, a process requiring functional lysosomes (181). Further, genes that are involved in lysosome biogenesis, such as that encoding the transcription factor TFEB, which stimulates lysosome biogenesis, appear suppressed in the MYC-expressing P493-6 cell line (182). The curbing of the activities of organelles that are not critical for cell growth, such as lysosomes, underscores the coordinating activity of MYC in stimulating growth. The role of MYC in the Golgi apparatus or nuclear formation is not well understood.

MYC, metabolism, and cell cycle progression

As organelle biogenesis proceeds to support growth, nucleotide pools accumulate in preparation for entry into S phase and DNA synthesis. MYC, however, does not only indirectly regulate the cell cycle through metabolism, it also directly triggers cell cycle progression, particularly during the G1 restriction point, by activating genes such as cyclin D and cyclin-dependent kinase 4 (CDK4) (183–186). In addition, MYC activates the expression of E2F transcription factors, creating a feed-forward loop that promotes progression into S phase (187). MYC and E2F together activate key DNA replication genes, such as the family of minichromosome maintenance complex (MCM) genes, to initiate and sustain DNA replication (140, 188). The induction of the microRNA cluster, miR-17-92, by MYC attenuates E2F1 function as cells enter S phase, seemingly to adjust the rate of DNA replication. Elimination of the miR-17-92 loop results in DNA replication stress following serum-induced MYC expression and cell proliferation (189, 190). In addition, MYC may have roles in initiation of DNA replication independent of its transcriptional activities, as it has been noted to localize to early sites of DNA replication and bind numerous components of the pre-replicative complex (191). The coupling of G1 to S-phase entry involves glycolysis and glutaminolysis in synchronized HeLa cells, which are known to have high MYC expression (192–194). Progression in the G1 phase toward S phase requires glycolysis and the activity of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), which is inactivated by the anaphase-promoting complex/cyclosome-Cdh1 (APC/C-Cdh1). Beyond the restriction point, committed HeLa cells appear dependent on glutaminase (GLS), which was also shown to be inactivated by APC/C-Cdh1 as cells progress from S to G2/M phase (193). We surmise then that accumulation of nucleotides and entry into S phase are coupled to ensure that DNA replication occurs with the highest fidelity, since nucleotide pool imbalance can result in undesirable mutations (195).

Oncogenic MYC-mediated metabolic rewiring and cancer therapy

The very first notable success in targeting metabolism for cancer therapy involves the use of anti-folates by Sidney Farber to effectively treat childhood acute lymphocytic leukemia (ALL) with aminopterin in 1948 (196). Farber, knowing that folates stimulated bone marrow and leukemic cell growth, sought anti-folates and pioneered clinical studies that first failed

with pteroylglutamic conjugates of folate—because these were in fact folate agonists rather than antagonists. The emergence of the antagonist, aminopterin, from the laboratory, however, transformed the treatment of childhood ALL with significant numbers of temporary clinical remissions in the initial 16 children who were treated. One of the children, Einar Gustafson who remained in remission and was the initial 'Jimmy' that inspired the extant fundraising Jimmy Fund, in fact, had the MYC-driven malignancy, Burkitt's lymphoma (196). Aminopterin inhibits dihydrofolate reductase (DHFR), and it is now replaced by methotrexate and more potent derivatives that are still mainstays in the cancer therapeutic armamentarium. As discussed above, the production of single carbon folate compounds requires the production of serine from glucose through a series of enzymes whose genes are directly regulated by MYC (122–124). Moreover, the sensitivity of human cancer cell lines to methotrexate has been linked to the MYC target gene signature and specifically to genes that are involved in folate metabolism (123).

As previously discussed, endogenous and ectopic MYC share many common targets that are involved in metabolism. The key question, then, is whether oncogenic MYC rewires metabolism distinctly from endogenous MYC. As noted early, endogenous normal MYC expression is upregulated only when growth factor signaling is activated and nutrients are available. Either growth factor withdrawal or nutrient insufficiency can inhibit endogenous MYC expression. These feedback loops, however, are ineffective to control MYC expression when it is deregulated, for example, by chromosomal translocation or gene amplification. In instances where the feedback loops are broken, deregulated MYC enforces a constitutive cellular growth program independent of nutrient availability, particularly when accompanied by loss of checkpoints such as TP53. While MYC driven metabolism in normal cells can be turned off by lack of either growth factors or nutrients, cancer cells that are unable to turn off MYC, are addicted to nutrients such as glucose and glutamine (Figure 5A–D). While the metabolic programs are generally similar in cells expressing low levels of MYC and high levels of MYC (197)(Figure 5E), the addiction of constitutive MYC activated cancer cells to metabolism creates therapeutic vulnerabilities.

With this framework in mind, it is surmised that loss of specific enzymatic activities would be synthetically lethal to MYC-overexpressing cells. Indeed, a screen using human fibroblasts overexpressing MYC revealed that loss of glucose metabolism genes (*ALDOA* and *PDK1*), nucleotide metabolism genes (*CTPS*), or transporters (*SLC1A4* and *SLC25A6*) were synthetically lethal (198, 199). A recent limited screen for synthetic lethality aimed at the extended MYC transcription factor network revealed that MONDOA (178), a partner of MLX, is required for MYC-overexpressing cells. MLX binds the MXD proteins, which in turn interact with the MYC partner MAX, thus extending the MYC network (1). Because MONDOA had been linked to regulation of glucose metabolism, investigators performed a synthetic lethal screen directed at MONDOA and MYC target genes involved in metabolism (178). This revealed that individual losses of genes encoding glutamine/glutamate transporters (*SLC1A5* and *SLC3A2*), purine metabolism enzymes (*PFAS* and *CAD*), cystathionine-beta-synthase (*CBS*), a mitochondrial transcription factor (*TFAM*), a glycolysis enzyme (*ENO3*), and lipogenesis enzymes (*FASN* and *SCD*) were synthetically lethal for MYC-overexpressing cells (178). These studies collectively indicate that MYC-

overexpressing cells are metabolically addicted; hence, small molecule inhibitors of specific enzymes could be potentially applicable in cancer therapy.

Because MYC drives both glycolysis and glutaminolysis *in vitro* and in various *in vivo* models, targeting glycolytic and glutaminolytic enzymes has been of significant research interest. Knockout of hexokinase 2 (*Hk2*) in genetically engineered mice significantly blunts tumorigenesis in vivo, suggesting that HK2 is an attractive therapeutic target (200). Genetic inhibition of LDHA using siRNA, for example, diminishes tumor growth in several models of tumorigenesis including one driven by MYC (201–203). Genetic knockout of *Ldha* also diminishes tumorigenesis in transgenic models of cancers (204, 205). A tool compound that inhibits LDHA was documented to inhibit a MYC-driven lymphoma xenograft (206). Because other oncogenes could also cause glycolytic addiction, inhibition of LDH or LDHA could have a broad-based application across many cancers. To this end, there have been many attempts to generate new LDH inhibitors (207–211).

Pharmacological inhibition of glutaminase (GLS) has also been documented to curb tumor progression of an inducible MYC-driven human lymphoma xenograft model in a cell-autonomous fashion (212, 213). Further, loss of one copy of murine *Gls* decreases MYC-induced liver tumorigenesis, and a tool-compound inhibitor of GLS prolongs survival of these mice(214). These studies provided the foundation for the development of a drug-candidate glutaminase inhibitor that is now undergoing Phase I clinical studies in humans (215). Likewise, inhibition of the lactate exporter MCT1 can significantly inhibit MYC-mediated lymphomagenesis, and MCT1 inhibitors are likewise in clinical trials (132). NAMPT, an enzyme involved in NAD^+ synthesis and a target of MYC, could also be another significant clinical target considering that the NAMPT inhibitor FK866 can profoundly inhibit MYC-induced lymphomagenesis and proliferation of lymphoma cell lines driven by other oncogenes (206). Additional inhibitors of NAMPT are being developed and some have already been studied clinically (216). Thus, it appears that MYC and potentially other oncogene-driven cancers are dependent on metabolic enzymes that could be explored and exploited for cancer therapy. In this regard, PIK3CA-, BRAF-, and RAS-driven cancers are dependent on MYC, such that resistance mechanisms to targeted inhibitors may result from MYC amplification or re-wiring of cellular metabolism (217–219). Given the extent to which cancer cells rewire metabolism, it stands to reason that combination therapy would be the most promising metabolic inhibition strategy in the clinic. For example, combination strategies, such as PI3K and MYC inhibition for breast cancer, BRAF and mitochondrial Complex I inhibition (phenformin) for melanoma, BRAF and pyruvate dehydrogenase inhibition for melanoma, mTOR and glutaminase inhibition for glioblastoma, and HSP90 and glutaminase inhibition for mTOR activated cancer, appear to have profound preclinical impact on tumorigenesis (220–223). This exciting area of cancer metabolism research has generated deeper and richer understanding of the relationships between oncogenic drivers and metabolism that will guide the field toward successful clinical applications of basic discoveries.

Conclusion and future outlook

MYC has been an enigmatic oncogene in that it seems to affect all cellular processes, most prominently cell metabolism and ribosome biogenesis. At the molecular level, this enigma could be resolved by considering evidence that suggests MYC is a general modulator of gene expression with its targets dictated by binding-site sequence affinity and chromatin accessibility and its directionality and magnitude of impact determined by the transcriptional potential of gene loci that are co-regulated by other transcription factors. All cells, including stem cells, are metabolically active and basally express metabolic genes whose chromatin is open. Thus, quiescent stem cells in the proliferative compartments of tissues are poised to proliferate upon stimulation by growth factors that trigger MYC expression. Upon such MYC activation, metabolic genes, which are already expressed, are further amplified to support the bioenergetic needs of the growing cell in its exit from the stem cell pool and differentiation down a cell lineage. Normal MYC is restrained in this role not only by growth factor presence but also nutrient availability. Oncogenic MYC, on the other hand, not only drives metabolic genes already regulated by endogenous MYC, but—owing to its deregulated expression—appears to invade enhancer sequences that further amplify gene expression in a non-linear fashion. This skewed gene-expression amplification leads to non-stoichiometric expression of biochemical pathways, activation of the unfolded protein response (UPR) pathway, and dependence on MONDOA, which all render MYC-overexpressing cells susceptible to synthetic lethality when specific metabolic pathways are inhibited. Here, basic science research in cancer metabolism has led to a number of new insights and identification of therapeutic opportunities, which hopefully will prove to advance the treatment of cancer patients. The field now looks to a future of new drugs targeting metabolism, which in combination with other drugs and modalities hold the promise of being impactful in the clinic.

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Statement of Significance

MYC's expression and activity are tightly regulated in normal cells by multiple mechanisms, including a dependence upon growth factor stimulation and replete nutrient status. In cancer, genetic deregulation of MYC expression and loss of checkpoint components, such as TP53, permit MYC to drive malignant transformation. However, because of the reliance of MYC-driven cancers on specific metabolic pathways, synthetic lethal interactions between MYC overexpression and specific enzyme inhibitors provide novel cancer therapeutic opportunities.

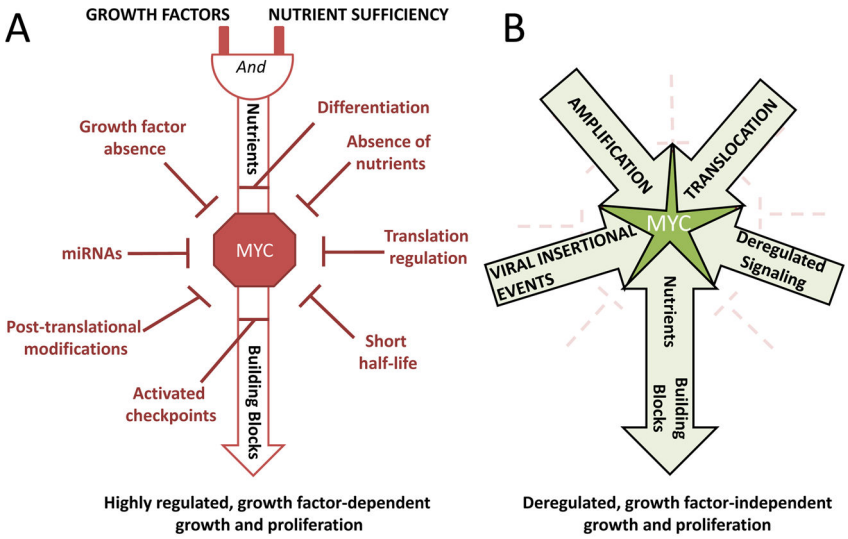

Figure 1. Schematic illustration of growth factor-dependent and growth factor-independent MYC activity

A) In non-cancerous cells, growth signals and adequate nutrients are required for MYC activity. Multiple levels of feedback loops and checkpoints further control MYC activity. B) In cancerous cells, in contrast, checkpoint loss, gene amplification, chromosomal translocation, abnormal enhancer activation, or one or more other deregulated signaling events lead to growth factor-independent MYC metabolic activities and subsequent unconstrained cellular growth and proliferation.

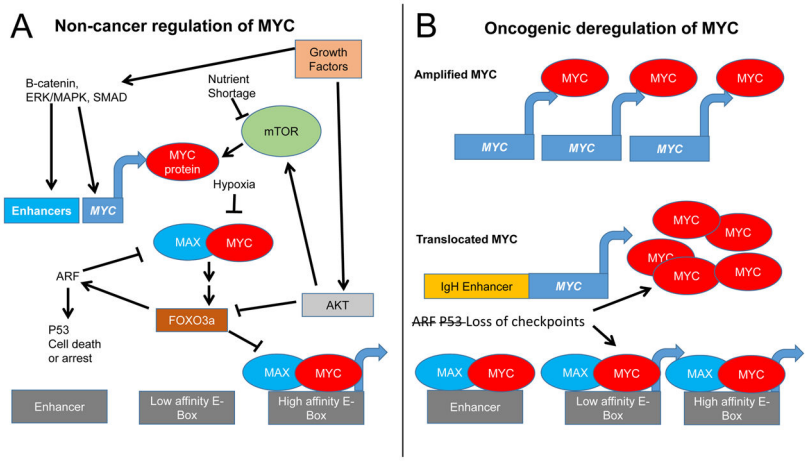

Figure 2.

MYC regulation in non-cancerous and cancerous cells. A) In non-cancerous cells *MYC* expression is activated by growth factors through activation of enhancers. MYC protein, whose translation is enhanced by activated mTOR, dimerizes with MAX to form a heterodimer that activates transcription of genes containing high affinity E-boxes. Upon nutrient shortage or hypoxia, MYC translation, protein stability and MYC/MAX dimerization inhibited. Over-activation of MYC activates the ARF and p53 checkpoints resulting in cell death or arrest, while ARF can inhibit MYC function. Downstream of AKT, FOXO3a proteins counteract MYC activation. B) In cancer cells, constitutive activation of growth factor and mTOR signaling, loss of checkpoints, engagement of atypical enhancers, or amplification or translocation of *MYC* can increase levels of MYC to supraphysiologic levels independently of growth factors, causing MYC/MAX binding to lower affinity binding sites and enhancers in addition to high affinity sites. Loss of ARF or p53 checkpoints allows uncontrolled cell growth.

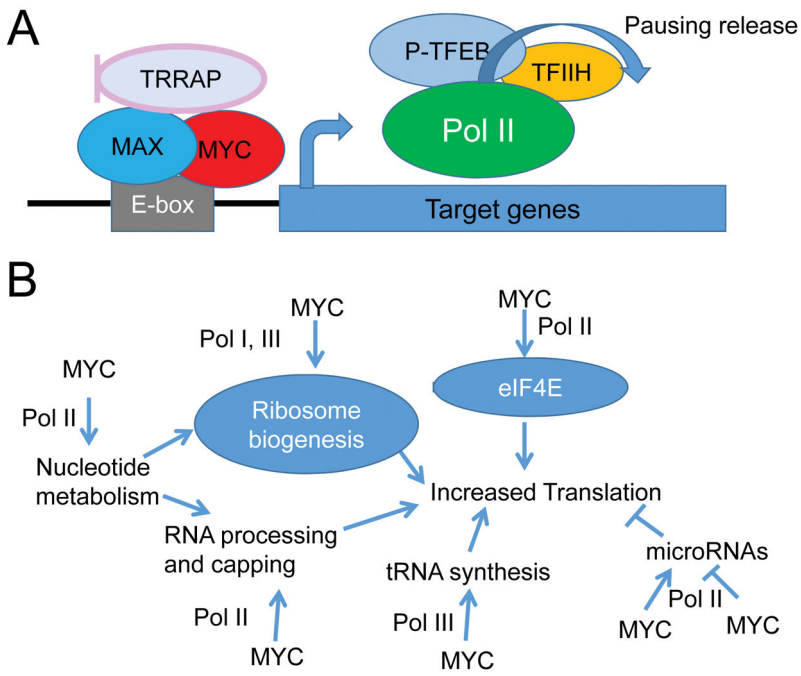

Figure 3.

MYC enhances transcription and translation. A) The MYC/MAX dimer binds to E-boxes or lower affinity degenerate sequences to recruit histone acetylases or promote polymerase phosphorylation, thus release polymerase from pausing to amplify transcription. B) Acting on Pol I, Pol II and Pol III, MYC controls translation through upregulation of transcription of ribosomal subunits, tRNA, and nucleotide synthesis genes. MYC also stimulates translation by upregulating eukaryotic translation initiation factor 4E (eIF4E) and stimulating enzymes that control RNA processing and capping. MYC upregulation and downregulation of microRNAs also regulates the translation of microRNA targets.

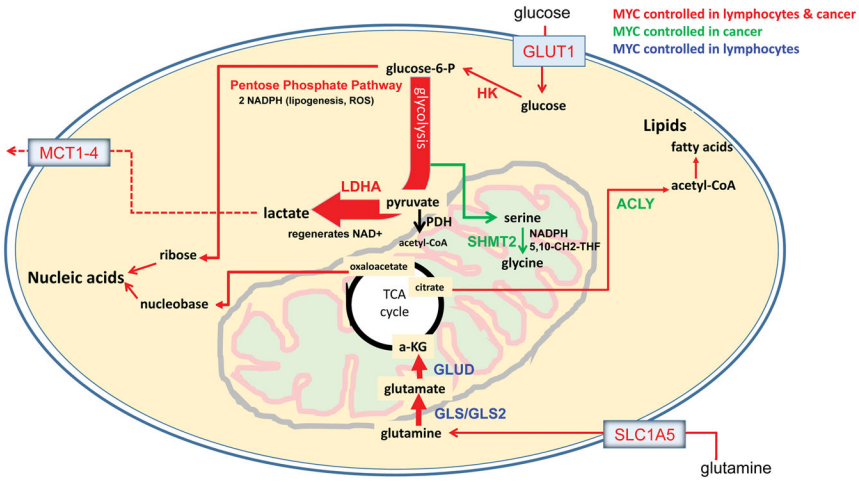

Figure 4.

Myc-regulated metabolic pathways in cancer. Glucose is taken up by glucose transporters (GLUT) and phosphorylated by hexokinase (HK) to form glucose-6-phosphate (glucose-6-P). Glucose-6-P can then either enter glycolysis or the pentose phosphate pathway, which supports nucleotide synthesis by yielding two NADPH reducing equivalents and one ribose per molecule of glucose. The serine biosynthesis pathway branches off glycolysis, producing serine and glycine that likewise support nucleotide synthesis. Serine hydroxymethyltransferase 2 (SHMT2) converts serine to glycine which, in a series of coupled reactions, can be used to create nucleotide and epigenetic methyl donor 5,10-CH2-tetrahydrofolate and mitochondrial NADPH for redox control. Lactate dehydrogenase (LDHA) can regenerate NAD^+ by converting glycolysis-derived pyruvate to lactate, which is then exported out of the cell by monocarboxylate transporters (MCT1-4). Alternatively, pyruvate can enter the TCA cycle in a pyruvate dehydrogenase (PDH)-dependent conversion to acetyl-CoA. TCA cycle citrate can be exported to the cytoplasm where it is converted to acetyl-CoA by ATP citrate lyase (ACLY). Cytoplasmic acetyl-CoA can then be channeled into lipogenesis. In addition to glucose, glutamine is an important fuel source in cancers. Glutamine is transported across the membrane by the glutamine transporter (SLC1A5/ASCT2) and converted to glutamate by glutaminase (GLS or GLS2). Glutamate can then be converted to the TCA cycle intermediate α-ketoglutarate (αKG) by glutamate dehydrogenase (GLUD) or aminotransferases.

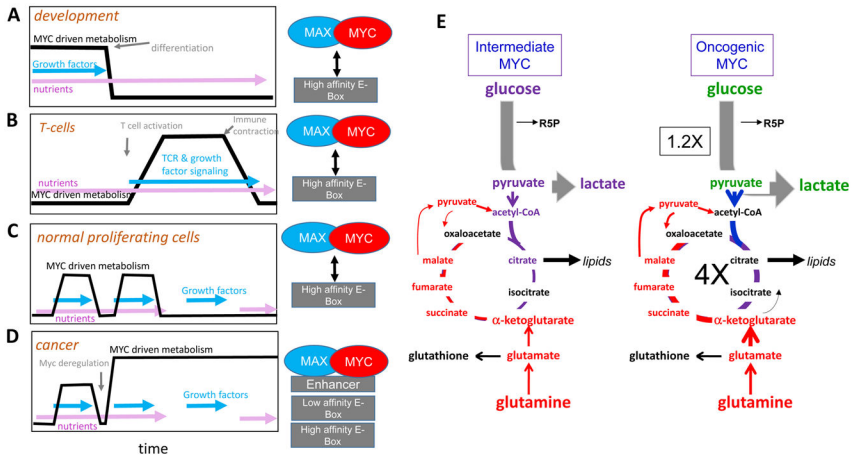

Figure 5.

The effect of nutrient and growth factor availability on MYC driven metabolism. A) During cellular differentiation, loss of growth factor stimulation can turn off MYC- driven metabolism even in the presence of nutrients. B) In T cells, receptor stimulation and growth factors can drive MYC signaling, but withdraw of receptor stimulation and checkpoints turn off MYC-driven metabolism even in the presence of nutrients. C) In normal proliferating cells, MYC-driven metabolism is activated in the presence of both nutrients and growth factors, but individual exposure to nutrients or growth factors is not sufficient to activate MYC-driven metabolism. D) In cancer, MYC deregulation and loss of checkpoints leaves cells unable to turn off MYC-driven metabolism independent of growth factors and nutrient availability. The inability to turn off MYC-driven metabolism creates therapeutic vulnerabilities to metabolic inhibitors. E) Comparison of glucose and glutamine metabolism of cells expressing intermediate levels of MYC and oncogenic levels of MYC shows oncogenic levels of MYC cause small increase (1.2 fold) in lactate production and a large increase (4 fold) in TCA cycle flux (197).