Cancer Cell
Minireview

HIF and c-Myc: Sibling Rivals for Control of Cancer Cell Metabolism and Proliferation

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DOI 10.1016/j.ccr.2007.07.006

O_2 deprivation (hypoxia) and cellular proliferation engage opposite cellular pathways, yet often coexist during tumor growth. The ability of cells to grow during hypoxia results in part from crosstalk between hypoxia-inducible factors (HIFs) and the proto-oncogene c-Myc. Acting alone, HIF and c-Myc partially regulate complex adaptations undertaken by tumor cells growing in low O_2. However, acting in concert these transcription factors reprogram metabolism, protein synthesis, and cell cycle progression, to "fine tune" adaptive responses to hypoxic environments.

Tumor signaling pathways regulating energy production and macromolecular synthesis have recently garnered substantial interest. Proto-oncogenes such as c-Myc direct changes in metabolism and protein synthesis supporting enhanced proliferation rates. At the same time, hypoxia and other environmental stresses (e.g., growth factor or nutrient deprivation) redirect intermediate metabolites, sustaining bioenergetics and cell survival. Recent studies describe crosstalk between the c-Myc and HIF pathways, demonstrating an interplay between responses to oxygen (O_2) deprivation and a key transcription factor regulating growth (Gordan et al., 2007; Koshiji et al., 2004; Zhang et al., 2007). In this review, we summarize the effects of c-Myc and HIFs on carbon metabolism, protein synthesis, and proliferation, highlighting their antagonist effects on carbon utilization and translation initiation. We will also describe direct effects of HIFs on c-Myc transcriptional activity.

In normal cells, c-Myc is induced upon growth factor stimulation, whereas it is constitutively high in transformed cells. Some degree of c-Myc overexpression is estimated to occur in 70% of human tumors. While c-Myc genomic amplification and translocation gives rise to extremely high protein levels, its upregulation more typically results from altered signal transduction and is therefore more modest (Nilsson and Cleveland, 2003). c-Myc acts as both a transcriptional activator and repressor, promoting transcription (e.g., *cyclin D2* and *ornithine decarboxylase* [*ODC*]) by binding E boxes (CACGTG) in a complex with Max, while inhibiting the expression of other genes (e.g., cyclin-dependant kinase inhibitors [CKIs] *p21* and *p27*) by binding their initiator elements in a complex with Max and Miz1 or Sp1. A second group of transcription factors, including Mad1 and Mxi, also bind E box sequences in a complex with Max but repress transcription. Myc family members L-Myc and N-Myc have also been identified. They regulate overlapping targets but have not been assessed for modulation by the HIFs and will not be discussed here (Adhikary and Eilers, 2005).

During rapid cellular proliferation, tumors outstrip their blood supply, limiting O_2 and nutrient availability. HIF-α subunits are continuously transcribed and translated, but degraded under normoxia due to prolyl hydroxylase activity, marking them for recognition by the von Hippel-Lindau (VHL) tumor suppressor ubiquitin ligase complex and proteasomal degradation. Under hypoxia (typically below 3%–5% O_2), HIF-α subunits are stabilized, translocate to the nucleus, dimerize with the stable β-subunit ARNT, and promote O_2-regulated gene expression. HIF-1α and HIF-2α, the best characterized HIF-α subunits, are differentially expressed: HIF-1α is ubiquitously expressed and HIF-2α is restricted to endothelial, lung, renal, and hepatic cells (Wiesener et al., 2003), although it has been observed in tumors of other tissues (Semenza, 2003). While HIF-1α and HIF-2α have shared targets, such as *vascular endothelial growth factor* (*VEGF*) and *adipose differentiation-related protein* (*ADRP*), they also regulate unique gene targets, with HIF-1α regulating glycolytic enzymes (Hu et al., 2003), and HIF-2α activating the stem cell factor *oct4* (Covello et al., 2006). HIF has been recently reviewed (Kaelin, 2005; Semenza, 2003); we focus here on the metabolic outcomes of HIF stabilization. We will refer to effects of both HIF-α subunits as HIF-mediated, whereas those unique to HIF-1α versus HIF-2α will be described separately.

Carbon Metabolism

Growth factors induce coordinated transcriptional, translational, and posttranslational changes to support cell cycle progression, increasing nutrient uptake and glycolytic metabolism. The resulting elevation in glucose metabolism occurs despite adequate O_2 for mitochondrial oxidative phosphorylation, a more efficient form of ATP production (Bauer et al., 2004). Pyruvate is produced at a higher rate than it is metabolized by mitochondria, with excesses converted to lactate by Lactate Dehydrogenase (LDH-A).

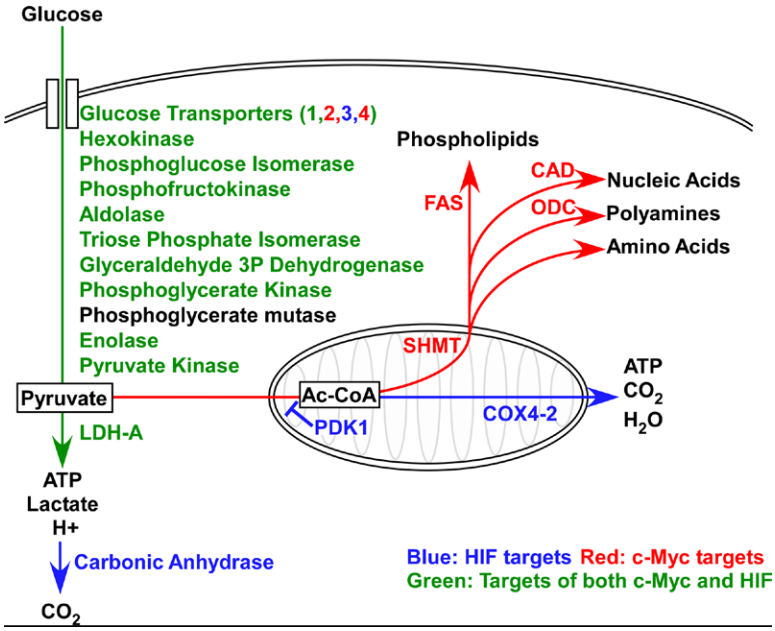

Figure 1. Schematic of HIF and c-Myc Effects on Carbon Metabolism

Both HIF and c-Myc act on multiple targets to regulate carbon utilization. HIF targets are shown in blue, c-Myc targets are shown in red, and targets regulated by *both* HIF and c-Myc are shown in green. Arrows are included to designate effects on flux through cellular pathways, with blue arrows showing pathways promoted by HIF, red arrows showing those promoted by c-Myc, and green arrows showing promotion by both.

In transformed cells, high levels of c-Myc promote energy production and biomolecule synthesis required for rapid proliferation, independent of growth factor stimulation. c-Myc enhances the glycolytic pathway, increasing target gene expression from glucose transporters through *pyruvate kinase* (listed in Figure 1), as well as *LDH-A*, allowing efflux of glucose-derived carbon as lactate (Osthus et al., 2000; Shim et al., 1997). Interestingly, LDH-A knockdown has been shown to inhibit transformed mammary epithelial cell proliferation in vitro and in subcutaneous allografts, possibly by promoting mitochondrial respiration (Fantin et al., 2006). While diverting pyruvate away from mitochondria, c-Myc increases mitochondrial mass through targets such as *mitochondrial transcription factor A* (*TFAM*), and increased mitochondrial iron metabolism (Li et al., 2005; Wu et al., 1999).

Why does c-Myc both promote mitochondrial biogenesis and shift metabolism toward glycolysis? c-Myc drives anabolic pathways, with targets including *carbomyl phosphate synthetase aspartate transcarbomylase and dihydroorotase* (*CAD*), *serine hydroxymethyltransferase* (*SHMT*), *fatty acid synthase* (*FAS*), and *ODC*, promoting nucleotide, amino acid, fatty acid, and polyamine synthesis (Coller et al., 2000; O'Connell et al., 2003). Each process requires mitochondrial intermediates. The importance of mitochondrial biosynthesis in c-Myc effects has been confirmed genetically: growth inhibition in c-Myc null fibroblasts is partially rescued by SHMT expression, producing carbon units for purine and amino acid synthesis (Nikiforov et al., 2002). Similarly, the polyamine synthetic enzyme ODC has been shown to be required for c-Myc-mediated lymphomagenesis (Nilsson et al., 2005). Therefore, while the enhanced glycolysis maintains ATP levels, growth promotion by c-Myc also requires mitochondrial activity to produce biosynthetic substrates.

HIF-1α/ARNT dimers also potently enhance glycolytic metabolism (Figure 1) with targets from glucose transporters through LDH-A (Hu et al., 2003). In contrast to c-Myc, HIF specifically blocks access of glycolytic end products to mitochondria. This effect is mediated by the HIF target Pyruvate Dehydrogenase Kinase 1 (PDK1), which inhibits conversion of pyruvate to acetyl-CoA by phosphorylating Pyruvate Dehydrogenase (Kim et al., 2006; Papandreou et al., 2006). At the same time, HIF mediates a shift in the components of cytochrome *c* oxidase (COX), substituting COX4-2 for COX4-1 via transcriptional upregulation of COX4-2 and the LON protease (which degrades COX4-1; Fukuda et al., 2007). This results in enhanced electron transport chain (ETC) efficiency under hypoxia, with increased ATP production and decreased ROS generation. HIF-2α/ARNT targets such as SOD2 also protect cellular and mitochondrial components in the presence of oxidative stress (Scortegagna et al., 2003), suggesting that ROS limitation is an important HIF metabolic adaptation to low O_2. Finally, by indirect modulation of c-Myc transcriptional activity (see below), chronic HIF activation decreases overall mitochondrial mass (Hervouet et al., 2005; Zhang et al., 2007).

By blocking pyruvate conversion to acetyl-CoA, HIF decreases anabolic use of glycolytic end products. This has been shown to inhibit de novo fatty acid synthesis (Lum et al., 2007). Similarly, HIF promotes the packaging of extracellular lipid into triglyceride droplets through ADRP, limiting its use in biosynthetic pathways (Bostrom et al., 2006). This should cause a metabolic shift even when c-Myc is present, as the anabolic pathways that c-

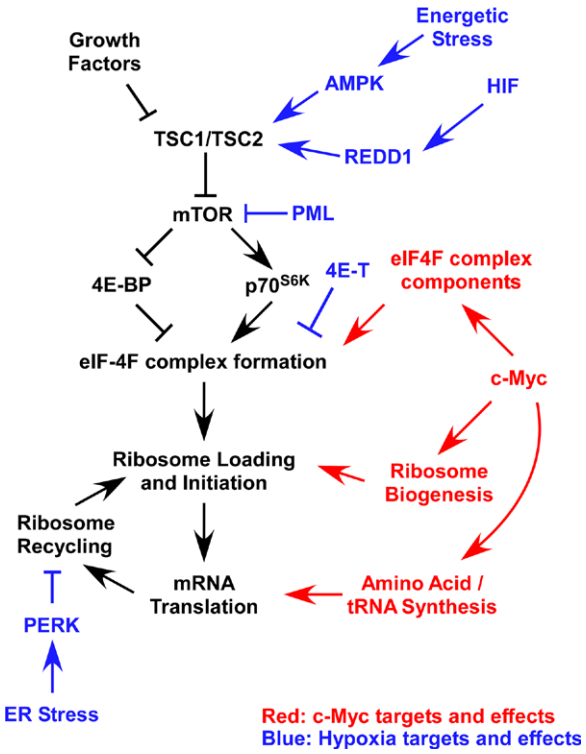

Figure 2. Hypoxic, HIF, and c-Myc Effects on Translation
While c-Myc promotes ribosome biogenesis and expression of components of the translational machinery, hypoxia and HIFs modulate growth factor signaling pathways that normally upregulate translation. c-Myc targets and c-Myc-promoted processes are highlighted in red, while direct HIF targets and hypoxia-promoted processes are shown in blue.

Myc upregulates are substrate limited. Thus, HIF blocks the energetically costly effects of c-Myc and helps tumor cells survive, while leaving c-Myc-directed biosynthetic pathways intact for use after reoxygenation.

Protein Translation

Cell division requires high levels of protein synthesis, effected by growth factor signaling pathway convergence on the tuberous sclerosis complex (TSC1 and TSC2), which regulates the mammalian target of rapamycin complex 1 (mTORC1). mTORC1 phosphorylates 4E-BP and p70 ribosomal protein S6 kinase ($p70^{S6K}$), promoting assembly of the eIF4F complex (eIF4A, eIF4E, and eIF4G), and initiation of cap-dependent translation. Supporting increased translation initiation (shown in Figure 2), c-Myc promotes ribosome and tRNA biogenesis through induction of the 45S pre-rRNA, tRNAs, and the 5S rRNA, enhancing Pol-I-dependent rRNA transcription through direct DNA binding, and associating with the Pol III component TFIIIB to increase tRNA and 5S rRNA levels (Arabi et al., 2005; Gomez-Roman et al., 2003; Grandori et al., 2005). eIF4F complex components eIF4E and eIF4G, as well as eIF2α (described below), are also c-Myc transcriptional targets (Coller et al., 2000; O'Connell et al., 2003).

Rather than regulating the expression of translation machinery components, O_2 deprivation results in HIF-dependent and HIF-independent inhibition of translation initiation (outlined in Figure 2). Anoxia (0% O_2) acutely induces eIF-2α phosphorylation (Koumenis et al., 2002) and causes eIF-4E sequestration in cytoplasmic P bodies by the 4E transporter (4E-T) with more delayed kinetics (Koritzinsky et al., 2006). Even mild hypoxia (1.5% O_2) triggers eIF-2α phosphorylation and 4E-BP and $p70^{S6K}$ hypophosphorylation (Arsham et al., 2003; Liu et al., 2006). eIF-2α phosphorylation, which blocks 43S preinitiation complex regeneration, is mediated by the endoplasmic reticulum resident kinase PERK independent of HIF (Koumenis et al., 2002). 4E-BP hypophosphorylation is downstream of mTORC1 inhibition resulting from AMP-activated kinase (AMPK) stimulation by energy depletion (Liu et al., 2006) and HIF induction of REDD1 (Brugarolas and Kaelin, 2004; Reiling and Hafen, 2004). REDD1 and AMPK both inhibit mTORC1 function via TSC2, although the mechanism by which REDD1 affects TSC2 is unclear. An additional HIF-independent effect on translation involves the PML tumor suppressor, where PML interacts directly with mTOR, disrupting its association with Rheb (Bernardi et al., 2006). In summary, hypoxia and HIF once again regulate substrate (in this case mRNA) access to biosynthetic machinery produced by c-Myc.

HIF Effects on c-Myc and Cell Cycle Control

c-Myc plays a central role in promoting G1 to S phase cell cycle transition by regulating cyclins and CKIs (Adhikary and Eilers, 2005). The hypoxic induction of HIF-1α suppresses cell proliferation: acute HIF-1α stabilization at moderate hypoxia (1% O_2) results in cell cycle arrest by inhibiting c-Myc transcriptional activity (Koshiji et al., 2004). In contrast, HIF-2α induction promotes cell cycle progression by enhancing c-Myc function (Gordan et al., 2007). It should also be noted that HIF-2α promotes Cyclin D1 expression in RCC but not other cells (Bindra et al., 2002).

HIF-1α and HIF-2α exhibit opposing effects on c-Myc interaction with its transcription cofactors, disrupting or stabilizing c-Myc DNA binding complexes, respectively. HIF-1α binds to Sp1, resulting in c-Myc displacement from Sp1 complexes and decreased c-Myc promoter interaction (Figure 3A, upper panel). Surprisingly, this occurs not only at the c-Myc repressed target p21 (Koshiji et al., 2004), where Sp1 is required, but also at c-Myc activated targets *MSH2*, *MSH6*, and *Nbs1* (Koshiji et al., 2005; To et al., 2006). The Per/Arnt/Sim (PAS)-B domain of HIF-1α mediates its interaction with Sp1. Though highly conserved in HIF-2α, the phosphorylation of threonine-324 in the HIF-2α PAS-B domain blocks HIF-2α/Sp1 association (To et al., 2006). However, HIF-2α forms a complex with Max, causing a dose-dependent stabilization of c-Myc/Max association (Figure 3B, upper panel), and increased c-Myc effects on the cell cycle regulators Cyclin D2, E2F1, p21, and p27 (Gordan

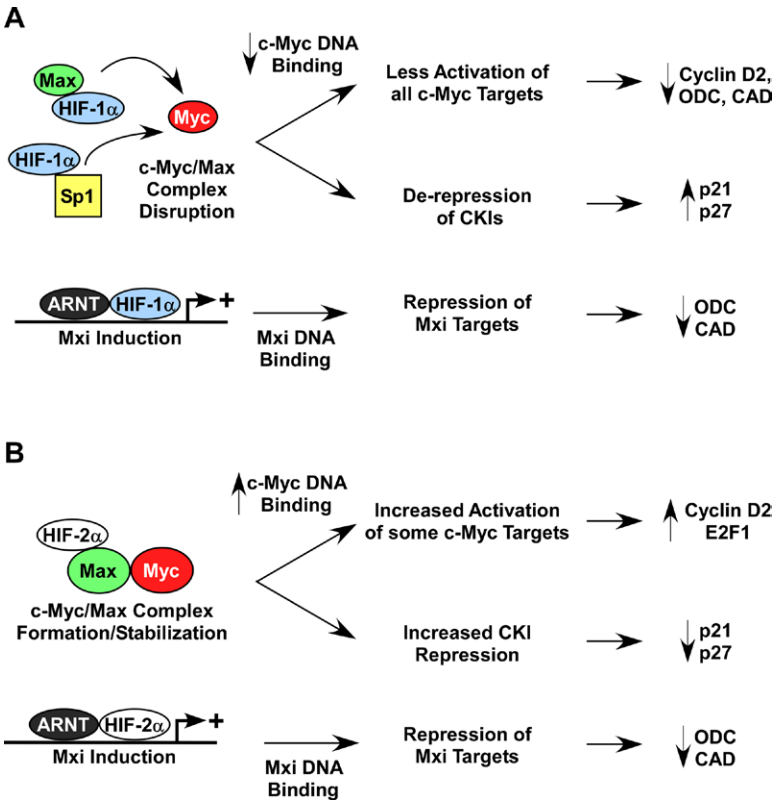

Figure 3. Acute and Chronic HIF Effects on c-Myc Transcriptional Activity

When HIF-1α is induced (A), it acts rapidly to disrupt c-Myc complexes. By inducing Mxi, it also causes transcriptional repression of some c-Myc target genes. Conversely (B), HIF-2α increases c-Myc transcriptional activity at specific targets, while inhibiting the expression of others via Mxi. By increasing c-Myc/Max interactions, HIF-2α promotes c-Myc-mediated activation or repression of *cyclin D2*, *p21*, and *p27*. However, Mxi induction inhibits expression of other c-Myc-activated targets (e.g., *CAD* and *ODC*).

et al., 2007). These growth-promoting effects of HIF-2α occur rapidly and are detected within 1–2 hr at 0.5% O_2. Furthermore, they are likely to be reversible. Competition for DNA-binding sites has been described, where HIF-1α binds sequences directly overlapping E boxes, blocking c-Myc DNA binding and inhibiting α-*fetoprotein* expression in HepG2 cells (Mazure et al., 2002).

Direct HIF-α effects on c-Myc transcriptional activity may be attenuated in c-Myc-overexpressing cells by altered c-Myc/Max stoichiometry. HIF-1α and HIF-2α effects on c-Myc targets and cell cycle progression have been described in nontransformed fibroblasts (Goda et al., 2003; Gordan et al., 2007) and in tumor cells where c-Myc is dysregulated, but not highly overexpressed. The effects of HIF on c-Myc have not been described for cells with massive c-Myc overexpression such as Burkitt's lymphoma but may be different in that context (C.V. Dang, personal communication).

A more chronic adaptation results from HIF-mediated Mxi induction causing decreased levels of c-Myc targets *ODC*, *CAD*, and *peroxisome proliferator-activated receptor gamma coactivator-1*β (*PGC-1*β; Zhang et al., 2007). This correlates with decreased apoptosis under anoxia (0.1% O_2), and decreased mitochondrial biogenesis (Corn et al., 2005; Zhang et al., 2007). Mxi interacts with Max and binds E boxes to inhibit transcription, an effect both necessary and sufficient to block transformation (Harper et al., 1996). Intriguingly, Mxi acts on only a subset of c-Myc targets, repressing ODC but not the DNA synthesis enzyme Ribose-5-Phosphate Isomerase (O'Hagan et al., 2000). As HIF-1α directly inhibits c-Myc transcriptional effects, hypoxic Mxi induction should reinforce HIF-1α effects, further decreasing c-Myc target expression (Figure 3A, lower panel). On the other hand, as HIF-2α can enhance c-Myc's effects on activated and repressed targets, Mxi is likely to repress a subset of c-Myc-activated targets (e.g., *PGC-1*β and *ODC*) while not interfering with HIF-2α effects on other c-Myc activated targets and on c-Myc repressed targets *p21* and *p27* (Figure 3B, lower panel). This may promote tumor cell survival by limiting c-Myc influences on energy-intensive processes and the production of toxic ROS, while causing increased proliferation rates.

Models for HIF/Myc Interplay in Tumors

Distinct expression kinetics contribute to HIF/c-Myc interplay in solid tumors. Tumor O_2 levels oscillate over both hours and days, causing periodic, fluctuating HIF expression (Dewhirst, 2007). While most tumors likely exhibit constitutively high c-Myc target gene expression, HIF-1α should transiently divert substrates away from anabolic synthesis and inhibit c-Myc transcriptional activity only when O_2 levels are dangerously low (<1% O_2). However, any appreciable effect on mitochondrial mass or metabolic enzyme expression following short periods of HIF activation is unlikely. Similarly, hypoxia disrupts the eIF-4F complex, temporarily inhibiting translation without dismantling the

translational machinery components. When O_2 levels return to normal, a tumor can then return to rapid proliferation under the influence of c-Myc. HIF-2α likely has different effects in tumors. For example, HIF-2α appears to be stabilized at higher O_2 levels (5%), and for longer time periods, than HIF-1α in neuroblastoma (Holmquist-Mengelbier et al., 2006). HIF-2α expression is also associated with worse prognosis than HIF-1α expression in some tumors (e.g., non-small-cell lung and head and neck cancer; Semenza, 2003). HIF-2α does not promote glycolytic metabolism and should not divert carbon away from mitochondria to the same extent as HIF-1α (Hu et al., 2003). This may allow it to promote angiogenesis while sparing c-Myc's effect on cell cycle progression.

In VHL-deficient renal tumors, the situation becomes more complex, partly because some renal tumors express different HIF-α subunits (Mandriota et al., 2002). Those expressing HIF-2α exclusively exhibit enhanced c-Myc-dependent proliferation, while HIF effects on mitochondrial metabolism should decrease O_2 consumption and ROS. When HIF-1α and HIF-2α are both present, they could antagonize each others' effect on c-Myc driven proliferation, while decreasing protein translation (through REDD1) and mitochondrial mass (via Mxi). In both cases, lipid accumulation is promoted, giving rise to the "clear cell" renal cancer phenotype. This is a very unusual metabolic status for a tumor and may result from dysregulation of novel players in tumor metabolism and growth that support proliferation independent of c-Myc.

ACKNOWLEDGMENTS

We thank Simon and Thompson lab members for useful discussions. This work was supported by NIH grants CA104838 and HL66130, and the Howard Hughes Medical Institute. We apologize to any colleagues whose work was not cited due to space constraints.

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