Published in final edited form as:
Cell Cycle. 2010 May ; 9(9): 1722–1728.

A therapeutic role for targeting c-Myc/Hif-1-dependent signaling pathways

Klaus Podar[1,2,*] and **Kenneth C. Anderson**[1]

[1] Department of Medical Oncology; Dana-Farber Cancer Institute; Harvard Medical School; Boston, MA USA

[2] National Center for Tumor Diseases (*NCT*); University of Heidelberg; Heidelberg, Germany

Abstract

Deregulated c-Myc occurs in ~30% of human cancers. Similarly, hypoxia-inducible factor (HIF) is commonly overexpressed in a variety of human malignancies. Under physiologic conditions, HIF inhibits c-Myc activity; however, when deregulated oncogenic c-Myc collaborates with HIF in inducing the expression of VEGF, PDK1 and hexokinase 2. Most of the knowledge of HIF derives from studies investigating a role of HIF under hypoxic conditions, however, HIF-1α stabilization is also found in normoxic conditions. Specifically, under hypoxic conditions HIF-1-mediated regulation of oncogenic c-Myc plays a pivotal role in conferring metabolic advantages to tumor cells as well as adaptation to the tumorigenic micromilieu. In addition, our own results show that under normoxic conditions oncogenic c-Myc is required for constitutive high HIF-1 protein levels and activity in Multiple Myeloma (MM) cells, thereby influencing VEGF secretion and angiogenic activity within the bone marrow microenvironment. Further studies are needed to delineate the functional relevance of HIF, MYC, and the HIF-MYC collaboration in MM and other malignancies, also integrating the tumor microenvironment and the cellular context. Importantly, early studies already demonstrate promising preclinical of novel agents, predominantly small molecules, which target c-Myc, HIF or both.

Keywords

HIF; c-Myc; targeted therapy; tumor microenvironment

Introduction

The basic helix-loop-helix leucine zipper (bHLH-LZ) transcription factor c-Myc regulates the expression of 10–15% of all genes of the genome.[1–5] In addition, it directly regulates DNA replication.[6] Deregulation of c-Myc occurs in ~30% of human cancers including breast, colon, cervical, small-cell lung cancer, osteosarcoma, glioblastoma, melanoma and myeloid leukemias; and is triggered by a variety of mechanisms including retroviral transduction, chromosomal translocation, gene amplification, as well as activation by hormones, their receptors, second messengers or transcriptional effectors.[7–14] Myc-containing pathways are therefore an attractive target for cancer therapy.

Hypoxia-inducible factor (HIF) is a prominent transcription factor, which, similar to c-Myc, both promotes and represses the transcription of a broad range of genes involved not only in

*Correspondence to: Klaus Podar; klaus_podar@dfci.harvard.edu, klaus.podar@med.uni-heidelberg.de.

angiogenesis but also in other aspects of cancer biology including tumor cell survival and proliferation, migration, pH regulation, metabolism, drug and radiation resistance, and immune evasion.[15] In addition, HIF-1 also promotes genetic instability by repressing transcription of the MSH2 and MSH6 genes via blockade of Myc-SP1 interaction. This effect does not require direct DNA binding or even the presence of HIF-1.[16]

In this review, we summarize the role of deregulated c-Myc and HIF in tumorigenesis in general, and MM in particular. Moreover, we focus on the proposed key pathophysiologic role of deregulated c-Myc-HIF collaboration in cell cycle progression, cell metabolism, DNA instability, as well as tumor angiogenesis. Finally, early preclinical data evaluating the role of derived novel agents targeting HIF-1 signaling are presented.

c-Myc

Functionally, c-Myc: (1) modulates cell cycle activity via blockade of transcription of cell cycle checkpoint genes (e.g., GADD45 and GADD153) and cyclin-dependent kinase (CDK) inhibitors, as well as promotion of cell cycle progression via activation of cyclin D1, D2, E1, A2, CDK4, cdc25A, E2F1 and E2F2; (2) stimulates differentiation and stem cell renewal; (3) induces as one of four factors the reprogramming of differentiated adult cells as one of four factors back to a pluripotent stem cell fate;[17] (4) increases cell metabolism via regulation of glucose transporter GLUT1, hexokinase 2, phosphofruktokinase and enolase, as well as via glutamine transporters (ASCT2 and SLC7A25) and glutaminase (GLS) due to repression of miR-23a/b;[18–21] (5) contributes to chromosomal instability and ROS production;[22–24] and (6) sensitizes cells to apoptosis. This last effect is triggered via an ARF-Mdm2-p53 tumor suppressor pathway which is regulated by BMI1, TWIST1 and CUL7; the induction of the pro-apoptotic BH3-only protein BIM; and BAX-mediated suppression of anti-apoptotic proteins Bcl-2 and BCL-X_L, followed by mitochondrial cytochrome *c* release. For example, Bcl-X_L gain of function and p19 ARF loss of function cooperate oncogenetically with c-Myc to induce tumors in pancreatic islet cells.[25,26]

As a regulator of transcription, c-Myc can work both as a transcriptional activator as well as a transcriptional repressor of target genes. In vivo, Myc heterodimerizes with Myc-associated protein X (MAX). Binding to E-box (CACAGTG) sequences, the Myc-MAX complex activates or represses gene transcription or modulates chromatin.[27,28] Transcription induced by the Myc-MAX complex is tightly regulated by the competitive complex formation of MAX with MAX dimerization proteins (MADs) Mad1, Mad2 (MAX interactor 1; MAXI1), Mad3, Mad4 and Mnt (Rox), followed by the subsequent recruitment of histone deacetylases (HDACs). Specifically, upon serum stimulation-enhanced c-Myc expression effectively competes with MAD for dimerization with MAX. c-Myc stability, and therefore expression and activity, is predominantly regulated by phosphorylation of residues Thr58 and Ser62. For example, activation of the Ras/MAPK/ERK pathway triggers phosphorylation of Ser62, thereby increasing Myc stability. When phosphorylated, Ser62 enables GSK3-mediated Thr58 phosphorylation, followed by FBW7/SCF/PP2A-dependent ubiquitylation and proteasomal degradation.[29–32] In addition, c-Myc activity is regulated by a short form of c-Myc,[33] a cap-independent translation of c-Myc,[34] and FOXO transcription factors.[35]

A requirement for transcriptional activation is the recruitment of co-activators including: positive transcription elongation factor b (P-TEFb); histone-acetyl-transferases (CREB-binding protein, CBP; p300; TRRAP; GCN5; TIP60); the ATPases TIP48 and TIP49; and the E3 ubiquitin ligase SKP2. Genes upregulated by Myc include HDAC2, CCND1, CCND2, CDK4, E2F2, LDHA and SHMT; whereas genes downregulated by Myc p21, p15, N-cadherins and integrins.[14,27] In contrast, Myc expression decreases due to limited

nutrients or high cellular density. In addition to E-box dependent transcription, c-Myc can also repress promoter activity by mechanisms independent from E-box binding sites, i.e., via nuclear factor Y (NF-Y), SP1 and Myc-interacting zinc finger 1 (MIZ1), TFII and yingyang-1. In summary, Myc-MAX heterodimers are predominant in proliferating cells; MAD-MAX and Mnt-MAX complexes are predominant in resting or differentiating cells.[36,37]

Besides directly coordinating multiple intracellular programs which mediate transformation, metabolic activity, and proliferation, c-Myc facilitates tumor cell growth via angiogenesis. Indeed, c-Myc has been postulated to be the master regulator of angiogenic factors, most prominently VEGF, and specifically of the angiogenic switch required for tumor progression and metastasis.[38–40] For example, targeted skin expression of c-Myc induces VEGF protein release and, in conjunction with hypoxia, further increases VEGF protein levels and angiogenesis.[41] Moreover, lethality in c-myc (−/−) mouse embryos is due at least in part to the requirement for c-Myc for VEGF expression, since VEGF can partially rescue defects in differentiation and growth, including vasculogenesis.[38,39]

In MM, complex karyotypic abnormalities of the c-myc locus are present in the majority of MM cell lines (reviewed in ref. 42). Rearrangements of c-Myc are reported in nearly 40% of advanced human MM. Enforced expression of c-Myc using Ig enhancers with peak activity in plasma cells recapitulates some features of human MM in a murine model.[43] Moreover, a conditional mouse model of sporadic MM strongly supports a pivotal role for c-Myc deregulation in the progression of benign MGUS to malignant MM.[44] Functional mechanisms of c-Myc mediating disease progression are not fully elucidated, and a role of c-Myc in triggering MM BM angiogenesis may be a contributing factor.[40,41,45]

Approaches to target c-Myc activity include inhibition of c-Myc/Max dimerization and blockade of c-Myc/Max binding to the DNA binding motif. Small molecules inhibiting Myc-Max dimerization include IIA6B17, NY2267, 10058-F4, and 28RH-NCN-1; small molecules inhibiting Myc-Max binding to DNA include the pyrazolo [1,5] pyrimidine Mycro1, 1 (Mycro3), Myra-A and NSC308848.[46–49]

HIF

HIF is composed of an oxygen-regulated-subunit and a constitutively expressed-subunit. Within the nucleus one of three HIF-1 subunits dimerizes with one of two isoforms of the subunit through the basic helix-loop-helix (bHLH) and PER-ARNT-SIM (PAS) A and B domains located in the N-terminal region of each subunit.[50] These dimers bind to specific DNA sequences within the promoter, intron and/or enhancer regions of target genes called hypoxia-response elements (HREs), which are composed of 5′-RCGTG-3′ and recruit co-activators.[51] Both HIF-1 and HIF-2 are overexpressed in common human cancers and their metastases.[52] Importantly, increased levels of HIF-1 or HIF-2 are correlated with adverse prognosis in breast, cervical, endometrial, colorectal, NSCLC, ovarian, rectal, pancreatic, and prostate cancers.[53–59]

Under normoxia, HIF expression is finely balanced between constitutive synthesis and proteasomal degradation.[60] Expression and activity of HIF-1, HIF-2 and HIF-3 are regulated via posttranslational prolyl-hydroxylase domain proteins (PHDs: PHD1, PHD2, PHD2)-mediated prolyl-hydroxylation of the oxygen-dependent degradation domain (ODDD)[61] and factor inhibiting HIF (FIH)-mediated asparaginyl-hydroxylation of the C-terminal end of HIF-1 and HIF-2 subunits.[62] Specifically, hydroxylation on proline residue 402 and/or 564 of HIF-1 by PHD2 mediates HIF interaction with the von Hippel-Lindau tumor suppressor protein (VHL). In turn, VHL protein recruits an E3 ubiquitin-protein ligase and catalyzes poly-ubiquitination of HIF-1α, thereby triggering its inactivation by proteasomal

degradation.[63] Asparaginyl hydroxylation of HIF-1 and HIF-2 prevents binding of co-activators p300 and CREB-binding protein (CBP), thereby inhibiting HIF activity.[61] Hydroxylation is dependent on the presence of oxygen, 2-oxoglutarate and cofactor FE^{2+}. Due to their decrease under hypoxic conditions, first PHDs and later FIH become inactivated, followed by full HIF activation due to inhibition of proteasome-mediated degradation and nuclear accumulation.[64,65] Moreover, transcriptional-activation domains (TADs), N-TAD and C-TAD in the C-terminus of HIF-1 and HIF-2 subunits regulate HIF transcriptional activity. Importantly and in contrast to N-TAD, C-TAD is inhibited by FIH hydroxylation thereby allowing bi-functional transcriptional activity of HIF-1.

Under hypoxia, reduced oxygen decreases the activity of PHDs and increases mitochondrial ROS release, thereby stabilizing HIF.[66] Besides hypoxia, HIF activation is also triggered via oxygen-independent mechanisms: autocrine growth factor stimulation including cytokines, lipopolysaccharides, EGF, FGF2, IGF; loss of tumor-suppressor function (LOF) including ING4, p53, PTEN and VHL; gain of oncogene function (GOF) including Ras, Raf, Src, PI3K/Akt, mTOR, Myc[15,52,67–69]; as well as reactive oxygen and nitrogen species.[70–72]

In MM, prior studies found that bortezomib inhibits tumor adaptation by stimulating factor inhibiting HIF-1 (FIH);[73] and that inhibitor of growth family member 4 (ING4) suppresses Hif-1 activity and angiogenesis under hypoxic conditions.[74] Moreover, *Asosingh* et al. have suggested an important role of HIF-1 and BM hypoxia in MM progression.[75]

Both conventional and novel therapies inhibit HIF-1 activity including doxorubicin,[76] geldanamycin/17-AAG, taxotere,[77] topotecan[78], imatinib,[79,80] gefitinib, erlotinib, cetuximab,[81,82] trastuzumab,[67] rapamycin, temsirolimus, everolimus[67,83] and histone deacetylase inhibitors.[84,85] Functionally, these compounds inhibit m-TOR-dependent translation of HIF-1 mRNA into protein, target HIF-1 for proteasomal degradation, and inhibit either HIF-1 transactivation domain function or HIF-1 transcriptional activity by blocking DNA binding.

More specific HIF-1 inhibitors include: (1) YC-1,[86–91] and PX-478, which inhibit Hif-1 expression provide radiosensitization to cancer cells including glioma, squamous cell, prostate and pancreatic adenocarcinoma cell lines in vivo.[92–94] A phase I clinical trial using PX-478 in advanced solid tumors or lymphoma has now been initiated (http://www.clinicaltrials.gov). (2) Polyamide 2,[95,96] which inhibits DNA binding and HIF-1 transcriptional activity by binding to the promoter of the HIF-1 target gene VEGF in nanomolar affinity; (3) NSC 50352, which blocks binding between the PAS-A domains of HIF-1 and HIF-1;[97] (4) acriflavine, an antimicrobial used in WWII, which similarly to NSC 50352 decreases the interaction between endogenous HIF1 and HIF1 under hypoxic conditions;[98] as well as (5) several compounds inhibiting HIF-PHD including oral FG-2216 and FG-4592;[99,100] and the antisense oligo-nucleotide against HIF1 EZN-2968.[101] A phase I clinical trial using EZN-2968 in advanced solid tumors or lymphoma has now been initiated (www.clinicaltrials.gov).

c-Myc and HIF

Under physiologic conditions Hif-1 inhibits c-Myc activity by direct interaction, induction of Mxi1, and stimulation of a proteasome-dependent pathway[102–104] however hypoaccentuates Myc-MAX-mediated transcriptional activation via Hif2-induced stabilization of Myc-MAX. Specifically, by increasing c-Myc/Max interactions, Hif-2 promotes c-Myc-mediated activation of cyclin D2, and triggers repression of p21 and p27.[104,105]

When deregulated, (oncogenic) c-Myc paradoxically collaborates with Hif-1. Specifically, c-Myc and Hif-1 collaborate in inducing the expression of PDK1 and hexokinase 2 followed by aerobic glycolysis (Warburg effect);[68,104,106,107] and VEGF (angiogenesis).[68,108]

Based on c-Myc/HIF-1 associated metabolic differences in normal versus cancer cells induced by the Warburg effect, LDHA and PDK1 have been identified as potential novel therapeutic targets.[109–112] Growth inhibition was also triggered by inhibition of another c-Myc/Hif-1 target gene, the transferring receptor gene (TFRC).[113,114] Moreover, echinomycin besides inhibiting DNA binding and transcriptional activity of HIF-1 also inhibits DNA binding of c-Myc/Max.[115,116] Furthermore, promising results were observed by targeting Hif-1/c-Myc-dependent glutamine metabolism using antisense mRNA against glutaminase, acivicin and BPTES.[117–119]

Given the importance of the BM microenvironment and BM angiogenesis in MM pathogenesis, we investigated the potential role of c-Myc and Hif-1 in triggering MM BM angiogenesis.[120] Our studies demonstrate that c-Myc and Hif-1 are elevated in all MM cells, even under normoxic conditions. Moreover, we identified a link between oncogenic c-Myc and Hif-1 expression, VEGF production and poor prognosis in MM patients. The particular novelty of our data was the demonstration that Hif-1α protein level and activity in MM cells under normoxic conditions is regulated by oncogenic c-Myc to influence VEGF secretion and angiogenic activity. These data are consistent with previous studies in other tumor models.[40,41,45,68,71] However, in contrast to previous data,[121–123] our data demonstrate c-Myc-dependent regulation of HIF-1 instead of the HIF-1α-dependent c-Myc regulation. In addition, our study identified c-Myc, HIF-1α, and the collaboration between both as a potential new therapeutic approach in MM. Using a drug screen we identified adaphostin, bortezomib, lenalidomide and enzastaurin to decrease HIF-1 levels and VEGF, dependent on c-Myc. Our in vitro results were then translated into in vivo demonstrating anti-angiogenic activity of our tool compound adaphostin[124] using the zebrafish model. To further enhance the clinical relevance of this model, we are now establishing a xenograft zebrafish model for MM, similar to those previously described for other cancers.[125] In summary, our study delineated a new c-Myc/Hif-1-dependent pathway, which triggers the release of VEGF and the induction of MM angiogenesis. It thereby supports the hypothesis that oncogenic c-Myc triggers MM progression, at least in part, by modulation of tumor angiogenesis.

Supporting our own data, inhibition of Hif-1 function by echinomycin or siRNA against Hif-1 resulted in enhanced sensitivity to melphalan in MM cells.[126] Taken together these studies strongly indicate a potential therapeutic role for targeting the c-Myc/Hif-1 pathway in MM and other solid tumors and hematologic malignancies.

Conclusions

When acting alone, the transcription factors HIF and c-Myc play a complex roles in tumorigenesis by regulation of tumor cell metabolism, cell cycle progression and angiogenesis. Importantly, in contrast to HIF-induced c-Myc inhibition under physiologic conditions, deregulated c-Myc forms a functionally synergistic complex with HIF, which fine-tunes the cellular homeostasis of tumor cells i.e., adaptation to hypoxia, cell metabolism, pH regulation and angiogenesis.[68,127] However, molecular sequelae underlying this synergism are elusive. One mechanism could be that high levels of c-Myc overcome the competing complex formation between c-Myc and Hif-1 through mass effect.[68,128,129] Another mechanism could be the induction of genomic instability via a Hif-1-induced release of the transcription factor Sp1, which in turn inhibits c-Myc-induced expression of MSH2 and MSH6.[130] Moreover, a recent study demonstrates that c-Myc decreases hypoxia-associated factor (HAF), which is responsible for oxygen-independent Hif-1

degradation.[131,132] Finally, distinct binding partners, co-activators and repressors, may be differentially recruited dependent on the presence of deregulated c-Myc as well as the cellular and microenvironmental context.

Most of the knowledge of HIF derives from studies investigating a role of HIF under hypoxic conditions; however, HIF-1α stabilization is also found under normoxic conditions. To date, mechanisms mediating HIF stabilization are still elusive, NFKB has been proposed as a direct modular of HIF-1α expression.[133] Our own data surprisingly demonstrate that deregulated c-Myc regulates Hif-1 levels in MM cells under normoxic conditions and thereby influences VEGF secretion and angiogenic activity within the bone marrow.[120] In ongoing studies, we are therefore investigating c-Myc-dependent molecular mechanisms leading to the maintenance of Hif-1 levels in the MM cell including transcriptional, translational and post-translational modifications. Importantly, adaphostin inhibits both HIF and c-Myc in a clinically relevant in vivo murine xenograft model of human MM providing the framework for evolution of novel therapies functionally similar to adaphostin.

Although HIF is predominantly associated with tumor progression and poor clinical outcome, a recent study demonstrates that HIF-1 might also have tumor suppressive activity, via induction of mir-210 both in normoxic and hypoxic cells. Indeed, overexpression of mir-210 in pancreatic and head and neck cancer cell lines delayed tumor cell growth in a murine xenograft mouse model.[134] Similarly and in contrast to our own data,[120] Noguera recently showed that high Hif-1 levels correlate negatively with advanced clinical stage and tumor vascularization in neuroblastoma.[135] One hypothesis for these discordant results may be tumor dependency, given the requirement for deregulated c-Myc in the tumorigenic c-Myc/Hif-1-complex, the anti-tumor effect in tumors lacking deregulated c-Myc remains to be evaluated. Moreover, further studies are needed to further delineate effect in cells that express Hif-1 and Hif-2, molecules with opposite effects.[136]

As our knowledge on the functions of c-Myc and HIF and their intimate punctional interaction grows, more efficient ways to target their molecular sequelae, dependent on the cellular context and on the tumor microenvironment, will be identified. Derived drugs have already demonstrated preclinical activity and are now in early clinical testing.

Acknowledgments

This work was supported by a National Institutes of Health Grants RO CA50947, PO-1 CA78378, and P50 CA100707; and the Doris Duke Distinguished Clinical Research Scientist Award (to K.C.A.).

Abbreviations

HIF	hypoxia-inducible factor
MM	multiple myeloma
VEGF	vascular endothelial growth factor
PHDs	prolyl-hydroxylase domain proteins
VHL	Hippel-Lindau tumor suppressor protein

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