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MYC on the Path to Cancer

Chi V. Dang[1,*]
[1]Division of Hematology-Oncology, Department of Medicine, Abramson Cancer Center, Abramson Family Cancer Research Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
*Correspondence: dangvchi@upenn.edu
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The *MYC* oncogene contributes to the genesis of many human cancers. Recent insights into its expression and function have led to therapeutic opportunities. *MYC*'s activation by bromodomain proteins could be inhibited by drug-like molecules, resulting in tumor inhibition in vivo. Tumor growth can also be curbed by pharmacologically uncoupling bioenergetic pathways involving glucose or glutamine metabolism from Myc-induced cellular biomass accumulation. Other approaches to halt Myc on the path to cancer involve targeting Myc-Max dimerization or Myc-induced microRNA expression. Here the richness of our understanding of *MYC* is reviewed, highlighting new biological insights and opportunities for cancer therapies.

Introduction

MYC belongs to a family that includes *MYCL* (L-Myc) and *MYCN* (N-Myc) (Brodeur et al., 1984; Kohl et al., 1984; Maris, 2010; Nau et al., 1985). Whereas the role of L-Myc is less well understood, N-Myc expression is tissue restricted, and N-Myc can substitute for c-Myc in murine development (Malynn et al., 2000). The protooncogene *MYC* lies at the crossroads of many growth-promoting signal transduction pathways and is an immediate early response gene downstream of many ligand-membrane receptor complexes (Armelin et al., 1984; Kelly et al., 1983) (Figure 1A). *MYC* expression is highly regulated, such that its level of expression is tightly control by a number of mechanisms involving many transcriptional regulatory motifs found within its proximal promoter region (Brooks and Hurley, 2010; Hurley et al., 2006; Levens, 2010).

The road to *MYC*'s discovery was paved by early studies of fulminant chicken tumors caused by oncogenic retroviruses, leading to the identification of the *v-myc* oncogene that causes *my*elocytomatosis (leukemia and sarcoma) (Duesberg and Vogt, 1979; Hu et al., 1979; Sheiness and Bishop, 1979). The *v-myc* oncogene was co-opted from the host cellular genome containing the protooncogenic version or *c-myc* (Vennstrom et al., 1982). Although the search for comparable human retroviruses failed to recapitulate the retroviral oncogene paradigm in human cancers, the discovery that human *MYC* is consistently altered by balanced chromosomal translocation in Burkitt lymphoma marked it as a bona fide human oncogene (Dalla-Favera et al., 1982; Taub et al., 1982). *MYC* is frequently translocated in multiple myeloma (Shou et al., 2000) and is one of the most highly amplified oncogenes among many different human cancers (Beroukhim et al., 2010). Defects in the Wnt-APC pathway found in human colon carcinoma result in enhanced TCF transcriptional activation of *MYC* (He et al., 1998). *MYC* is downstream of deregulated Notch signaling pathways found in T cell leukemia (Palomero et al., 2006; Sharma et al., 2006; Weng et al., 2006). Hence, alterations of *MYC* are commonly found on the path to cancer.

In addition to its role in tumorigenesis, *MYC* was also identified as one of four genes, including *Sox2, Oct4,* and *KLF4*, that could collectively reprogram fibroblasts to a pluripotent stem cell state (Laurenti et al., 2009; Singh and Dalton, 2009; Takahashi and Yamanaka, 2006). Given its pivotal role in cell growth, proliferation, tumorigenesis, and stem cells, it appears timely to review what is currently understood about *MYC* by addressing the following key questions. What are the molecular functions of its protein product, Myc? How does *MYC* contribute to tumorigenesis? What are the differences between the *MYC* protooncogene and its deregulated form found in a variety of human cancers? Could *MYC* or Myc's target genes be targeted for cancer therapy?

Myc, Checkpoints, and Neoplastic Transformation

Early in vitro studies of *MYC* revealed its potential to transform normal embryonic fibroblasts in cooperation with other oncogenes (Land et al., 1983). These studies set the stage for transgenic mouse studies that provided the evidence that deregulated expression of *MYC* is sufficient to drive tumorigenesis in a number of transgenic mouse tissues (Adams et al., 1985; Chesi et al., 2008; Leder et al., 1986). Retroviral insertional mutagenesis further identified c-Myc as a major murine oncogene (Akagi et al., 2004). In each of these models, however, additional mutagenic events are necessary for tumor formation as evidenced by a predictable time delay before the onset of tumors (Beer et al., 2004; Ellwood-Yen et al., 2003; Felsher and Bishop, 1999a; Pelengaris et al., 1999). Hence, *MYC* requires other genetic alterations in vivo to enable its tumorigenic potential. Mammary carcinomas triggered by transgenic Myc expression acquire K-ras mutations that render tumors aggressive (D'Cruz et al., 2001). Acute overexpression of Myc in normal cells triggers checkpoints including ARF or p53 (Figure 1B), such that many *MYC*-induced transgenic lymphomas lack functional Arf or p53 (Eischen et al., 1999; Zindy et al., 1998). The findings from transgenic mouse studies underscore a causal role for *MYC* in murine cancers and support its tumorigenic role in human cancers.

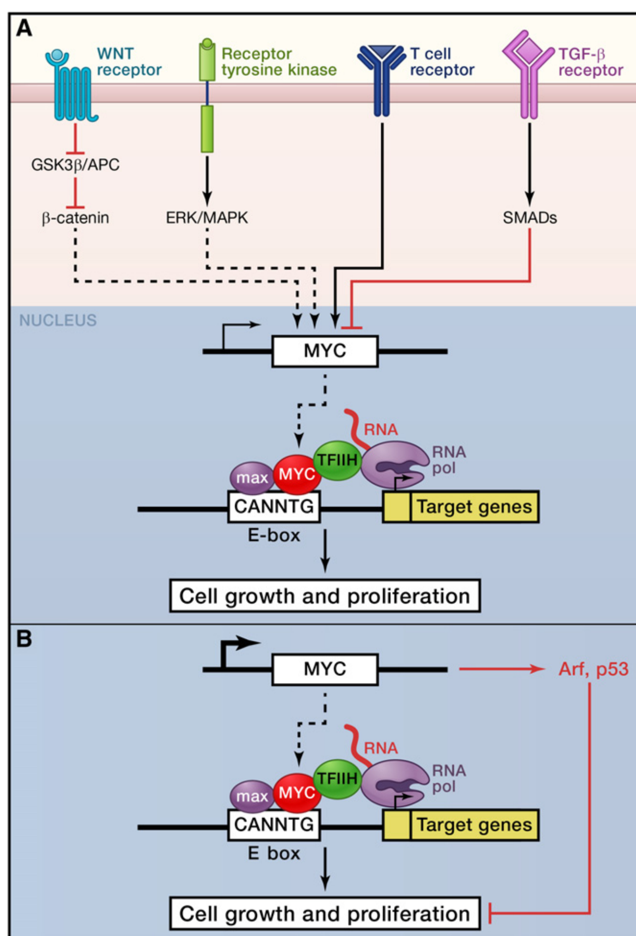

Figure 1. Myc Regulates Cell Growth and Proliferation

(A) The *MYC* protooncogene is depicted downstream of receptor signal transduction pathways, which elicit positive or negative regulation of the *MYC* gene. *MYC* produces the transcription factor Myc, which dimerizes with Max and binds target DNA sequences or E boxes (with the sequence 5′-CANNTG-3′) to regulate transcription of genes involved in cell growth and proliferation. The WNT pathway is depicted with APC negatively regulating β-catenin, which upon nuclear translocation participates in the transactivation of *MYC*, such that loss of APC results in constitutive oncogenic *MYC* expression.

(B) When *MYC* is deregulated, by gene amplication, chromosomal translocation, or loss of upstream regulators, such as APC, acute sustained oncogenic *MYC* expression results in checkpoint activation of p53 or Arf. Loss of checkpoint regulation through mutations of p53 or Arf, for example, uncloaks *MYC*'s full tumorigenic potential.

MYC is documented to play a role in tumor initiation; however, whether it also participates in tumor maintenance had previously been unclear. Knockdown of *MYC* in established cancer cell lines in vitro appears to uniformly reduce cell proliferation and in some instances induce apoptosis (Cappellen et al., 2007; Koh et al., 2011a; Wang et al., 2008). In transgenic mouse models with inducible *MYC*, established tumors regress upon withdrawal of *MYC* ectopic expression, indicating that it plays a role in tumor maintenance, and once established these tumors are addicted to *MYC* (Arvanitis and Felsher, 2006). In fact, expression of a dominant-negative inhibitor of Myc heterodimerization in vivo has resulted in tumor regression, suggesting that inhibiting Myc function could be a feasible therapeutic strategy (Soucek et al., 2008).

Molecular Functions of Myc

The *MYC* mRNA generates Myc polypeptides, including one that initiates at a CUG upstream of the canonical AUG start codon and another that starts at an internal AUG (Blackwood et al., 1994). The Myc protein translated from the canonical AUG contains an N-terminal transcriptional regulatory domain followed by a nuclear localization signal and a C-terminal region with a basic DNA-binding domain tethered to a helix-loop-helix-leucine zipper (HLH-Zip) dimerization motif. Myc dimerizes with Max to bind DNA and mediates many of its functions (Amati et al., 1992, 1993; Blackwood and Eisenman, 1991; Grinberg et al., 2004; Kato et al., 1992; Kretzner et al., 1992). A distinct function for the longer Myc polypeptide initiated at the upstream CUG is not known (Blackwood et al., 1994; Hann et al., 1992), but the shorter one initiated from an internal AUG appears to play a role in stress response and perhaps serves as a dominant-negative Myc protein (Spotts et al., 1997; Xiao et al., 1998). Myc biology is further complicated by the finding that a cytoplasmic cleavage product of Myc (Myc-nick), which lacks the nuclear localization signal and DNA-binding domain, can promote alpha-tubulin acetylation by recruiting GCN5 and promote cell differentiation in a nontranscriptional manner (Conacci-Sorrell et al., 2010).

Myc also appears to recruit DNA replication licensing factors to catalyze DNA replication, although whether its transcriptional function at replication origins is part-and-parcel of its DNA replication activity is not yet clear (Dominguez-Sola et al., 2007). Myc also plays an important nontranscriptional role in stimulating cap-dependent translation (Cole and Cowling, 2008; Cowling and Cole, 2007). Lastly, Myc appears to function even in the absence of functional Max protein as documented in PC12 cells and more recently in *Drosophila* (Hopewell and Ziff, 1995; Steiger et al., 2008). Whether Myc could homo-oligomerize or hetero-oligomerize with other helix-loop-helix proteins to regulate transcription in the absence of Max in cells remains unknown (Nair and Burley, 2003).

The Myc protein contains an unstructured N-terminal transcriptional regulatory domain, which contains conserved Myc boxes I and II, followed by Myc boxes III and IV and a nuclear targeting sequence (Cowling et al., 2006; Dang and Lee, 1988; Kato et al., 1990; Pineda-Lucena and Arrowsmith, 2001). The C-terminal domain comprises a basic HLH-Zip domain, which is largely unstructured until it dimerizes with Max (Follis et al., 2009; Hu et al., 2005; Mustata et al., 2009; Sauvé et al., 2007). The monomers assemble on DNA, and the heterodimer locks onto and bends DNA through binding motifs (5′-CACGTG-3′) termed E boxes (Park et al., 2004). The N-terminal domain has been documented to form complexes with many factors including TRRAP, GCN5, and TBP, which are likely to induce more structured folding of the N-terminal Myc transcriptional regulatory domain (Fladvad et al., 2005; Liu et al., 2003; McEwan et al., 1996; McMahon et al., 2000; Nikiforov et al., 2002). Hence, it is envisioned that when bound to DNA, the Myc-Max heterodimer would recruit complexes that modify chromatin (Figure 2).

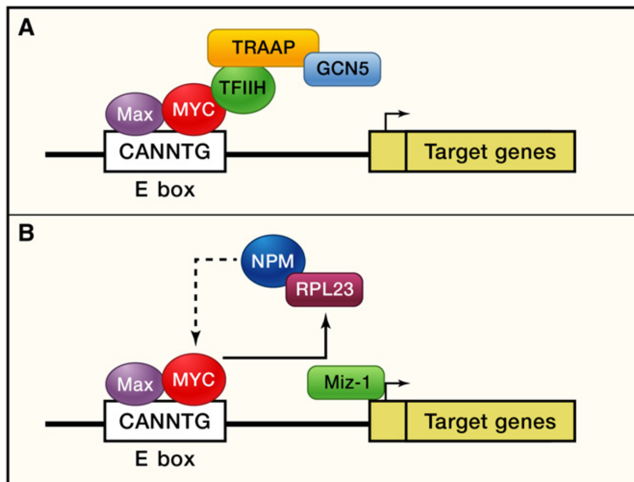

Figure 2. Myc-Max-Mediated Transcription and Gene Repression
(A) The Myc-Max heterodimer is shown to interact with key cofactors, such as transcription factor 2H (TFIIH) that triggers transcriptional elongation or transformation/transcription domain-associated protein (TRRAP) that recruits the GCN5, which acetylates histones, permitting transcription of target genes.
(B) Myc-Max also mediates gene repression. Miz-1 is shown tethered to the initiator (INR) element to regulate transcription of target genes, which could be silenced by Myc displacement of nucleophosmin (NPM), a Miz-1 cofactor, or Myc induction of the ribosomal protein RPL23, which retains NPM in the nucleolus, keeping it away from Miz-1.

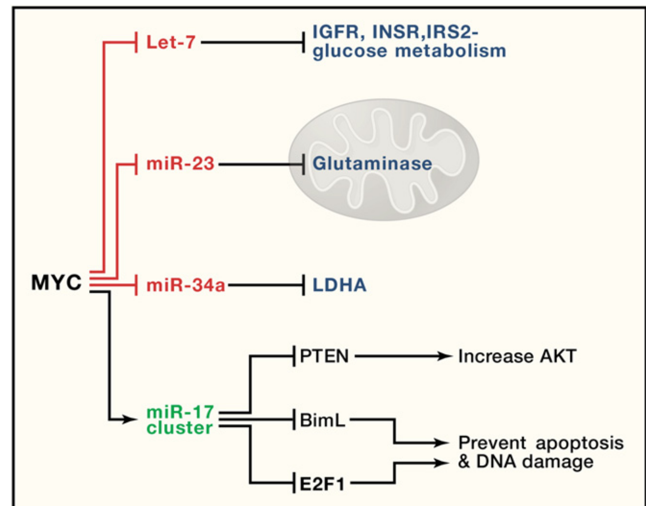

Figure 3. The Myc miRNA Network
Myc regulates a network of miRNAs through activation of the miR-17-92 cluster and repression of dozens of miRs including Let-7, which was recently shown to affect insulin signaling, miR-23a/b, which regulates glutaminase expression, and miR-34a, which was shown to regulate lactate dehydrogenase (LDHA) expression. The miR-17 cluster contains miRNAs that target PTEN, thereby activating AKT, and those that target proapoptotic BimL or transcription factor E2F1 expression. miRNAs downstream of Myc have also been implicated in EMT and angiogenesis.

Although the mechanisms by which Myc activates transcription, including the recruitment of histone acetylase, are emerging, the mode by which Myc represses gene expression is less well understood. Among the vast numbers of targets that are repressed by Myc, a fraction is linked to Miz-1, which activates these genes (Figure 2) (Schneider et al., 1997). TGF-β signaling best illustrates a role for the Myc-Miz-1 interaction. In the absence of TGF-β, Myc represses CDKN2B (p15INK4b) by binding Miz-1 and displacing Miz-1 cofactors to silence CDKN2B (Seoane et al., 2001). With TGF-β, *MYC* expression is suppressed, and the Smad transcription factor translocates and cooperates with Miz-1 to recruit NPM1 as a Miz-1 cofactor to stimulate CDKN2B transcription and induce cell-cycle arrest (Wanzel et al., 2008). Myc, on the other hand, activates many ribosomal protein genes including Rpl23, which binds to and retains NPM1 in the nucleolus, thereby inhibiting Miz-1 activity. Myc itself is modulated by NPM1, which acts as a positive Myc coactivator (Li et al., 2008).

Another critical mode for Myc-mediated gene repression is through its ability to activate microRNAs (miRNAs) (Figure 3) (Chang et al., 2008; O'Donnell et al., 2005). Specifically, the activation of the miR-17-92 cluster of miRNAs mediates a number of biological activities of Myc, including the attenuation of E2F1 activity. Intriguingly, the miR-17-92 cluster also targets many components of the TGF-β signaling pathway (Aguda et al., 2008; Dews et al., 2010; Mestdagh et al., 2010; O'Donnell et al., 2005). These observations indicate that Myc repression of gene expression occurs through different modalities that are linked to regulatory loops. Myc also represses many more miRNAs, resulting in increased gene expression at the protein level (Figure 3). It is almost certain that Myc would also directly activate long noncoding RNAs (lncRNAs) to mediate gene repression, as implicated in studies of embryonic stem cells (ESCs).

Transcription: Upstream and Downstream of Myc

The *MYC* protooncogene itself is under tight transcriptional control as are the mRNA and Myc protein. In fact, *MYC* is regulated not only by a whole host of transcription factors, such as CNBP, FBP, and TCF (which is downstream of the Wnt pathway), but also by non-B DNA structures including single-stranded bubbles, G-quadruplexes, and Z-DNA (Levens, 2010). The FUSE (*f*ar *u*pstream *e*lement) melts when bound by FBP (FUSE-binding protein), which relieves torsional stresses on DNA from ongoing transcription of *MYC* (He et al., 2000). TCF is a transcription factor that plays a role in deregulated *MYC* expression downstream of the WNT pathway, such as with the loss of the tumor suppressor APC that results in constitutive nuclear localization of the TCF cofactor β-catenin. Genome-wide association studies further identified common polymorphisms nearby *MYC* that are associated with multiple cancers (Ahmadiyeh et al., 2010; Tuupanen et al., 2009; Wasserman et al., 2010). Such single-nucleotide polymorphisms (SNPs) lie in enhancers that involve TCF binding and DNA looping, which connects the enhancer to the *MYC* proximal promoter (Pomerantz et al., 2009; Sotelo et al., 2010; Wright et al., 2010). Recently, the BET domain containing transcriptional regulator BRD4 was shown to bind to the *MYC* promoter region and play a critical role in *MYC* expression in human cancer cells such that a drug-like BET domain chemical inhibitor could inhibit in vivo tumorigenesis (Delmore et al., 2011; Mertz et al., 2011).

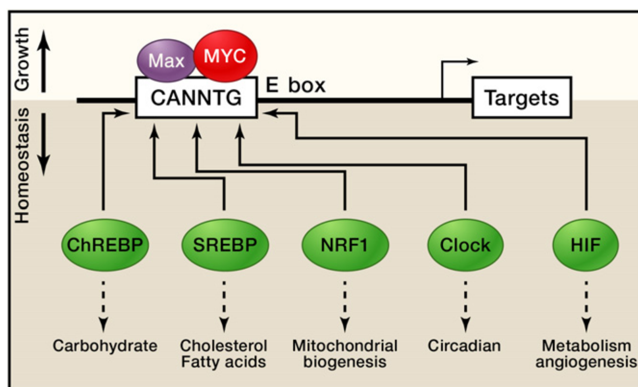

Figure 4. Homeostatic and Proliferative Regulation of E Box-Driven Genes

Myc-Max is shown bound to E box-driven genes, which could also be regulated by other E box transcription factors, such as the carbohydrate response element-binding protein (ChREBP), sterol response element-binding protein (SREBP), nuclear respiratory factor 1 (NRF1), circadian transcription factor Clock (and Bmal), and hypoxia-inducible factor (HIF). The non-Myc E box transcription factors regulate genes involved in metabolism, which is maintained for cellular homeostasis when cells are not proliferating. Upon activation of *MYC* and elevated levels of Myc, mass action favors the binding of Myc-Max to E box genes to regulate metabolism and genes involved in ribosomal biogenesis and cell mass accumulation. This model suggests that resting cells express metabolic genes through "homeostatic" E box transcription factors, which regulate a set of genes that overlaps with Myc target genes that are expressed when cells are stimulated to grow and proliferate.

The *MYC* mRNA, which is short lived, is affected by miRNAs (let-7, miR-34, and miR-145) resulting in translational modulation (Cannell et al., 2010; Christoffersen et al., 2010; Kim et al., 2009; Kress et al., 2011; Sachdeva et al., 2009). The Myc protein itself is posttranslationally modified, ubiquitinated, and degraded, with a half-life in the order of 15–20 min (Gregory and Hann, 2000; Gregory et al., 2003). Myc transcriptional activity is regulated by phosphorylation at Ser62 followed by Thr58 and subsequent proteasomal degradation after performing its function (Salghetti et al., 1999; Thomas and Tansey, 2011; Adhikary et al., 2005; Popov et al., 2007, 2010). Mutations of Myc residues Thr58 and Ser62, prevalently found in Burkitt lymphoma, are associated with stabilized mutant proteins that could perturb transgenic mammary tumorigenesis (Salghetti et al., 1999; Thomas and Tansey, 2011; Wang et al., 2011b). The resulting sustained levels of Myc contribute to tumorigenesis, which in some instances may not require total elevated average levels of Myc but rather depend on deregulated expression of Myc throughout the cell cycle. How then does Myc transcriptional activity contribute to tumorigenesis?

The canonical Myc E box 5′-CACGTG-3′ is among the most frequently occurring DNA-binding motifs in the human genome (Xie et al., 2005). This motif, however, could be bound by different transcription factors such as ChREBP, SREBP, HIF-1, NRF1, USF, TFE3, Clock, and Bmal (Figure 4). It stands to reason that in nonproliferating cells, non-Myc E box transcription factors regulate basal metabolism to maintain cellular structural and functional integrity. When cells are stimulated to proliferate, Myc levels rise, permitting Myc to occupy E box-driven genes normally bound by other transcription factors and activate a program of biomass accumulation and enhanced cellular bioenergetics. As such, which of the many E boxes are occupied by Myc in proliferating cells, and does occupancy trigger changes in transcription and mRNA levels of the target genes?

Genome-wide association of Myc protein to chromatin has been documented by a number of approaches. Myc was documented by chromatin immunoprecipitation (ChIP) and quantitative PCR to bind a selected panel of promoters (Fernandez et al., 2003). A genome-wide study in *Drosophila* documented key dMyc-bound target genes that are involved in many cellular functions, consistent with studies performed in mammalian cells (Orian et al., 2005); most notable among the Myc targets is the cyclin-dependent kinase CDK4, which is also a key target in mammals. Myc-binding sites were also mapped using a promoter array containing 4,839 promoter sequences (Li et al., 2003). This study suggests that Myc could be considered a general transcriptional factor because promoters (15%) were broadly bound by Myc. This study was corroborated by a subsequent ChIP-chip tiled array study of human chromosomes 21 and 22, which documented widespread association of Myc with chromatin (Cawley et al., 2004). Genome-wide Myc-binding sites were mapped in a human B cell line with ChIP followed by paired-ends tag sequencing (ChIP-PET) of the immunoprecipitated DNA fragments (Zeller et al., 2006). This study estimated that up to 6,000 genes are bound by Myc, and among the 3,000 genes deemed high-quality Myc-bound target genes, only about 700 genes responded to Myc activation with alterations in their mRNA levels. Most of these binding sites are found in the proximal promoter, with significant portions found intragenically, and about 10% located in intergenic (>100 kb from promoters) regions.

A subsequent study examines the role of Myc in transcription and relief of RNA polymerase (Pol) II paused complexes (Rahl et al., 2010). This study provides evidence suggesting that recruitment of pTEFb by Myc stimulates pause release partly by phosphorylation of RNA Pol II. This view is in contrast to the previous perspective that transcription factors such as Myc assemble cofactors, which in turn recruit TBP and RNA Pol II for transcription initiation. In this regard, it is intriguing to note that a significant proportion of Myc-binding sites occur in the first introns of genes. Although the position of Myc-binding sites and their effects on transcription pause release were not specifically addressed, this work establishes a key role for Myc in transcriptional elongation.

Genome-wide mapping of Myc-binding sites and associated gene expression profiling established that Myc binding is insufficient to induce changes in mRNA levels of target genes. In fact, many of the Myc-bound and -induced genes in the human B cell model are associated with E2F DNA-binding motifs, suggesting that Myc targets require additional factors for their expression (Li et al., 2003; Zeller et al., 2006). An instructive study of Myc among six other factors, including stem cell factors Sox2, Oct4, and KLF4, and their binding sites in murine ESCs revealed that genes whose expression is changed with stem cell differentiation tend to be those that were bound by multiple transcriptional factors (Kim et al., 2010). Hence, binding by a single transcription factor is generally insufficient to activate a target gene, unless it is bound by multiple transcriptional factors.

What then are the Myc target genes, and how do they contribute to the biology of the cell?

Myc Target Genes, Stem Cells, and the Path to Cancer

Although low-throughput approaches to identify and characterize Myc target genes were largely fruitful, a global perspective of Myc function has only recently emerged from unbiased studies of Myc targets. It is notable that early studies rely on changes in mRNA levels in response to manipulation of Myc levels to identify Myc target genes. Recently, the combination of global chromatin immunoprecipitation and gene expression profiling provides a better approach to defining Myc targets, particularly if coupled with a genome-wide nuclear run-on assay (Ji et al., 2011).

Through the use of an inducible Myc system coupled with ChIP-seq and gene expression changes, a set of 300 Myc-dependent serum response (MDSR) genes was identified in fibroblasts (Perna et al., 2011). This set comprises about 6% of Myc-bound targets, which encompass 22% of all promoters. Intriguingly, these MDSR genes are largely involved in nucleotide metabolism, ribosome biogenesis, RNA processing, and DNA replication. In this regard, Myc also regulates RNA Pol I- and Pol III-mediated transcription in addition to its role in regulating RNA Pol II genes (Felton-Edkins et al., 2003; Gomez-Roman et al., 2003; Grandori et al., 2005; Kenneth et al., 2007). Thus, the protein biosynthetic machinery is inherently linked to Myc transcriptional activity, and the balance between rRNA synthesis, ribosomal protein production, and the availability of adequate bioenergetics is essential for normal cell growth. Many direct Myc target genes encode ribosomal proteins, which are directly involved in the ARF and p53 checkpoint, particularly when ribosome biogenesis is perturbed.

A common 50 gene Myc core signature (MCS) was identified among Myc target genes in four tumorigenic human cell lines and in ESCs, and expression of the MCS correlates with *MYC* gene expression among 8,129 microarray samples that include 312 cell and tissue types, attesting to its cell-type independence (Ji et al., 2011). Functional annotation of the MCS reveals enrichment of genes involved in ribosome biogenesis, underscoring Myc's primordial function in biomass accumulation. This notion is consistent with the observation that diminished *Drosophila* dMyc function results in small cells and body size, which phenocopies mutations affecting ribosomal protein genes found in a large set of mutants termed Minutes (Johnston et al., 1999). Furthermore, the link between Myc and ribosome biogenesis has been documented in specific cell types (Challagundla et al., 2011; Chan et al., 2011; Greasley et al., 2000; Kim et al., 2000; Schlosser et al., 2005; Schlosser et al., 2003) and in Myc-driven tumorigenesis in vivo (Barna et al., 2008; Stumpf and Ruggero, 2011). It is long known that cancer cells are characterized by intense nucleolar hypertrophy; hence, a signature of cancer cells could now be linked mechanistically to Myc function (van Riggelen et al., 2010b).

The role of Myc in reprogramming fibroblasts to pluripotency and in stem cells emerges from a number of studies. One study suggests that Myc drives an ESC-like program, without defining the functional significance of this program (Wong et al., 2008). The study by Kim et al. (2010), however, dissected the roles of stem cell factors (Sox2, Oct4) versus Myc through ChIP analysis (Kim et al., 2010). In this case, stem cell factors regulate a distinct core stem cell module of target genes, whereas Myc drives a program common to ESCs and cancer cells but distinct from the core stem cell targets. A third genetic module comprises polycomb-related genes, which are involved in regulation of cell differentiation. The Myc module is enriched in genes involved in ribosome biogenesis, suggesting that the MCS does mark a core function of Myc (Kim et al., 2010). It is notable, however, that other studies implicate Myc in the regulation of chromatin structure, which is reprogrammed in stem cells. Myc induces Bmi-1 and EZH2, which are polycomb proteins, and perhaps modulates the expression of lncRNAs that are involved in polycomb-mediated gene silencing (Guney et al., 2006; Koh et al., 2011b; Sander et al., 2008). Perhaps, these Myc functions link Myc to the regulation of the polycomb module, the suppression of senescence, terminal cell differentiation, and the maintenance of pluripotency.

The role of Myc in tissue stem cells appears to depend on the tissue type, and multiple studies suggest that *MYC* is required for the commitment to terminal differentiation, which contrasts with the role of *MYC* in pluripotency. *MYC*'s roles in tissue versus pluripotent stem cells are expected to be different; however, additional studies are required to provide a richer mechanistic understanding. *MYC* is required for production of committed hematopoietic progenitors such that loss of *MYC* in mice results in the expansion of hematopoietic stem cells (HSCs) and diminished progenitors with pancytopenia (Laurenti et al., 2008). On the other hand, overexpression of *MYC* causes a decrease in the HSC pool. Similarly, skin stem cells and pro-B cells require Myc for differentiation to mature keratinocytes or B cells, respectively (Frye et al., 2003; Gandarillas and Watt, 1997; Habib et al., 2007; Iritani et al., 2002; Watt et al., 2008). Hence, transient Myc-induced cell proliferation is coupled with differentiation in multiple tissues in vivo. Although *MYC* is required for colonic epithelial turnover, deletion of *MYC* in mouse hepatocytes does not inhibit liver regeneration (Baena et al., 2005; Li et al., 2006; Sansom et al., 2007; Wilkins and Sansom, 2008). It remains unclear, however, whether N-Myc could play a role in the absence of c-Myc in the liver. These studies collectively indicate that Myc plays a critical role in tissue stem cell maturation toward committed progenitors.

The study of the 50 gene MCS also allows for an analysis of genes that are cell-type-specific Myc target genes (Ji et al., 2011). In this regard, B cell-restricted genes such as BLMH behave as a direct Myc target, and LIN28 behaves as a human ESC-restricted Myc target, whereas FBL is an MCS gene common to many cell types (Chang et al., 2009; Ji et al., 2011; Koh et al., 2011a). These studies collectively suggest that a key function of Myc is to drive biomass accumulation. Biomass accumulation requires a commensurate level of bioenergetics and building blocks, but genes involved in energy metabolism are not found in the MCS. This observation suggests that the bioenergetics of cells may depend on cell types. Among normal cells there is a remarkable array of different metabolic profiles, from highly aerobic (cardiac, brain) to adaptive anaerobic (skeletal muscle) cells. Hence, it could be the variable uses of different energetic pathways among different cell

types that eliminate Myc target genes involved in metabolism from the MCS.

Although the MCS defines a stringent cell-type-independent set of Myc targets, other bona fide Myc targets have been firmly identified in a number of systems. In fact, Myc directly regulates genes involved in cell-cycle regulation, such as CDK4, which is documented in mammalian and *Drosophila* cells as a Myc target (Hermeking et al., 2000; Orian et al., 2003). In addition, Myc regulates energy metabolism through its direct activation of genes involved in glycolysis, glutamine metabolism, and mitochondrial biogenesis (Gao et al., 2009; Li et al., 2005; Osthus et al., 2000; Shim et al., 1997; Wise et al., 2008). In this regard, it seems that Myc as a master regulator affects a broad spectrum of genes to coordinate energy metabolism with biomass accumulation in preparation for DNA replication and cell division. The cooperation of Myc with other transcription factors such as E2F is necessary for the sequential expression of target genes as the cell traverses through the cell cycle (Li et al., 2003; Pickering et al., 2009; Zeller et al., 2006). Under hypoxia, normal Myc can be suppressed by the hypoxia-inducible factor, HIF-1 (Gordan et al., 2007, 2008; Zhang et al., 2007); however, deregulated *MYC* expression appears to collaborate with HIF-1 to drive glycolytic gene expression for cancer cell proliferation (Dang, 2007; Kim et al., 2007; Qing et al., 2010). The ability of Myc or N-Myc to cooperate with HIF-1 could be highly relevant to the ability of cancer cells to survive and proliferate under moderately hypoxic conditions commonly found in the tumor microenvironment. This perspective suggests that normal cell proliferation is controlled by many of the same genes that are coordinated by Myc in cancer cells. The question then is whether there are distinctive features of normal *MYC* regulation of cell proliferation versus those related to oncogenic (deregulated) *MYC*.

Metabolic and *MYC* Oncogene Addiction

In contrast to normal cells, in which the *MYC* protooncogene is under stringent regulation downstream of many receptor signaling pathways, including WNT, Hedgehog, Notch, TGF-β, as well as many receptor tyrosine kinases, *MYC* activation in cancer cells can result from constitutive activation of a pathway, such as WNT in tumors with loss of APC, or through direct alterations of the *MYC* gene, such as amplification or chromosomal translocation. Furthermore, *MYC* amplification is documented as a means to resist therapeutic inhibition of PI3K, indicating that *MYC* is downstream of PI3K for tumorigenesis (Ilic et al., 2011; Muellner et al., 2011). The deregulated expression of *MYC* in cancers presumably causes a sustained increase in Myc protein expression, perhaps throughout the cell cycle rather than in a restricted manner. A threshold level for the pathological expression of Myc has been documented in several systems, supporting the concept that constitutive, elevated expression of Myc contributes to tumorigenesis (Murphy et al., 2008; Shachaf et al., 2008; Yustein et al., 2010). It is also reasonable to hypothesize that constitutive Myc expression could cause Myc to promiscuously activate E box-driven genes that would be regulated by other E box transcription factors in the normal nonproliferative cells.

It could be envisioned that nonproliferating cells express certain E box genes for homeostatic purposes. For example, lipogenesis in nonproliferating liver or fat cells is mediated by SREBP (Krycer et al., 2010). Mitochondrial biogenesis could be stimulated in normal cells by NRF1, which binds E boxes and is a target of Myc (Scarpulla, 2008). Certain E box-driven metabolic genes are regulated in a circadian rhythm by Clock/Bmal, whereas glycolytic and angiogenic genes can be activated by HIF-1 in response to hypoxia (Asher and Schibler, 2011; Semenza, 2007; Shchors et al., 2006). When Myc is elevated, it could bind to the same targets that would be bound by other E box transcription factors (Dang et al., 2008; Kim et al., 2007). Hence, it is plausible that there is a switch in the regulation of E box genes from homeostatic transcription to Myc transactivation, which orchestrates cell growth and proliferation. In this regard, the ability of Myc to co-opt the functions of other E box transcription factors would enable Myc to coordinate a growth program along with angiogenesis (Baudino et al., 2002; Dews et al., 2010; Knies-Bamforth et al., 2004). In the case of lipogenic genes, their induction by Myc would be for lipid membrane synthesis for a growing cell rather than for fat storage. Glycolytic and mitochondrial genes would be induced by Myc to drive the biosynthetic needs of proliferating cells. The metabolic gene NAMPT, which is involved in NAD^+ synthesis, is a circadian gene responsive to Clock/Bmal in the liver (Ramsey et al., 2009). The NAMPT gene is prominently bound by Myc and is a direct Myc target gene (Menssen et al., 2012). Collectively, these findings suggest that deregulated Myc commandeers many of the E box genes to enable the cell to grow and then divide, and in the case of neoplasia, Myc also drives angiogenesis (Figure 4).

Normal cells have feedback loops that negatively regulate growth when deprived of nutrients or growth factors. Deprivation of glucose from normal fibroblasts causes them to withdraw from the cell cycle into the G1 phase of the cell cycle (Holley and Kiernan, 1974). Perhaps this is due partly to the diminished levels of Myc under hypoxia or low-glucose conditions (Okuyama et al., 2010). Because glucose is involved in multiple metabolic pathways including glycolysis (providing carbon skeletons for lipid synthesis), the pentose phosphate pathway (ribose synthesis), and glucosamine synthesis, its deprivation is expected to profoundly affect normal cell proliferation. In contrast, glucose withdrawal of Myc-overexpressing cells triggers apoptosis (Shim et al., 1998). Likewise, glutamine withdrawal triggers apoptosis of Myc-overexpressing cells (Yuneva et al., 2007). In the recent study of normal primary activated murine T lymphocytes bearing floxed Myc alleles, it was found that the initial phase of cell growth (cell size increase) was profoundly dependent on Myc expression that drives target genes involved in both glucose and glutamine metabolism. Loss of Myc was associated with profoundly diminished expression of genes involved in metabolism and the inability for normal primary T cells to grow and proliferate (Wang et al., 2011a). It was also documented that HIF-1, which regulates anaerobic glycolysis, was not required for cell growth but required for T cell fate determination (Dang et al., 2011; Shi et al., 2011). Given that Myc drives biomass accumulation, the sensitivity of Myc-overexpressing cells to nutrient deprivation could reflect their deregulated growth, which renders them dependent on and addicted to continual bioenergetic sources, such as glucose and glutamine.

Although nutrient dependency characterizes a feature of Myc-transformed cells, it has been recognized in transgenic models that Myc-induced tumors are also addicted to Myc, such that conditional silencing of ectopic Myc expression causes tumor regression in a number of different tumor models. The collapse of the tumor microenvironment and neovasculature could account for the oncogene addiction (Giuriato et al., 2006; Sodir et al., 2011). In these cases, the time-dependent changes in the Myc-induced genetic program when Myc is turned off may cause an asynchrony between bioenergetics demands and fuel sources. Inactivation of Myc can also restore the normal TGF-β regulatory circuitry, such that loss of Myc would reactivate SMAD-Miz-1-mediated activation of p21 downstream of TGF-β, culminating in cell-cycle arrest and senescence (van Riggelen et al., 2010a). Finally, immune cells are critical components of the tumor microenvironment, and in this regard, they affect Myc's ability to regulate angiogenesis and senescence (Rakhra et al., 2010).

Conceptually, it appears that regulation of Myc expression in normal cells is orchestrated in a fashion that withdrawal of growth signals is followed by an orderly recession of gene expression programs such that there is a balance between fuel needs and fuel supply and utilization by the normal cell. In Myc-overexpressing transformed cells, deregulated Myc presumably alters expression and the balance among the target genes such that Myc withdrawal is followed by an asynchronous recession of the target gene network, resulting in an imbalance between nutrient supply and demand. In some cases, a brief suppression of *MYC* is sufficient to reverse in vivo tumorigenesis (Jain et al., 2002), but not in other cases (Boxer et al., 2004; Jonkers and Berns, 2004; Shachaf et al., 2004), suggesting that tissue specificity and either other mutagenic events or epigenetic alterations affect the reversibility of tumorigenesis upon Myc suppression. Suppression of *MYC* could trigger senescence or cause an imbalance between apoptotic and antiapoptotic gene expression and could also tip the scale toward cell death with Myc withdrawal (Felsher, 2010; Wu et al., 2007; Zhuang et al., 2008). It is reasonable to hypothesize that the imbalance between energy demand and supply upon Myc withdrawal could also play a role in Myc oncogene addiction.

Metastasis and Genome Instability Induced by Myc

Cancer cells are not just characterized by the propensity to proliferate with disregard to extracellular cues but also underscored by increased genomic instability, changes in morphology and function such as epithelial-mesenchymal transition (EMT), and an increased ability to metastasize. Given that Myc can repress genes involved in cell-cell and cell-substratum contacts and that these processes would be diminished as normal cells detach from neighboring cells to undergo mitosis, it should not be surprising that overexpressed Myc would also elicit these phenotypes (Dang et al., 2006). Myc has been linked to EMT and metastasis via its regulation of miRNA miR-9, which targets E-cadherin, as well as its ability to transactivate Bmi-1 which is linked to EMT (Ma et al., 2010; Song et al., 2009). Whether Myc plays a similar parallel role in nonpathologic conditions is not clear.

Overexpression of Myc in a number of cell systems in vitro has been linked to increased genomic instability (Felsher and Bishop, 1999b; Karlsson et al., 2003; Neiman et al., 2006; Prochownik, 2008; Ray et al., 2006). Myc induction of reactive oxygen species (ROS), presumably through its induction of mitochondrial biogenesis and increased metabolism, has been implicated in genomic instability (Egler et al., 2005; Gao et al., 2007; Vafa et al., 2002; Zhang et al., 2007). Here it could be envisioned that normal cells with normal regulated Myc would have the appropriate compensatory mechanisms to detoxify free oxygen radicals, whereas highly active Myc would induce a sustained ROS insult on the genome, causing instability (Egler et al., 2005; Graves et al., 2009; Wonsey et al., 2002). Whether ROS is central to Myc-induced genomic instability is unclear, particularly given that Myc could directly affect telomere function and increase genome instability (Louis et al., 2005). Intriguingly, in a transgenic lymphoma model with inducible Myc, many of the tumors display remarkable chromosomal rearrangements, suggesting that Myc affects chromosomal stability, but the molecular details remained undefined (Karlsson et al., 2003). Myc is, however, known to regulate a number of components of the mitotic checkpoint; whether deregulated expression of these components contributes to chromosomal instability remains to be studied (Li and Dang, 1999; Menssen et al., 2007).

Therapeutic Opportunities

MYC certainly seems to be at the crossroads of many important biological pathways and processes involved in neoplastic cell growth and proliferation. *MYC* is documented to be involved broadly in many cancers, in which its expression is estimated to be elevated or deregulated in up to 70% of human cancers. High levels of *MYC* expression have been linked to aggressive human prostate cancer and triple-negative breast cancer (Gurel et al., 2008; Palaskas et al., 2011). Experimental models of Myc-mediated tumorigenesis suggest that established tumors are addicted to Myc and that deregulated expression of Myc results in an addiction not only to Myc but also to nutrients. These Myc-induced changes provide a unique opportunity for new therapeutic strategies. Notwithstanding the fact that normal proliferating cells (stem cell compartments and immune cells) also use *MYC* for renewal, many studies have focused on targeting Myc for cancer therapeutics. Strategies have emerged to inhibit *MYC* expression, to interrupt Myc-Max dimerization, to inhibit Myc-Max DNA binding, and to interfere with key Myc target genes.

Although there has been significant attention to the G-quadruplex regulatory sequence in the *MYC* promoter as a therapeutic target, current available compounds that lock the G-quadruplex into an "off" mode are not yet shown to be effective in the preclinical setting (Brown et al., 2011; Dai et al., 2011). Intriguingly, the BET bromain domain regulatory proteins recently emerged as potent regulators of *MYC* expression in different tumor types. In particular, inhibition of BET with a drug-like molecule in multiple myeloma, a malignant plasma cell tumor, resulted in a remarkable diminution of *MYC* expression and associated cell death. In this regard, it is also notable that a number of Burkitt lymphoma cell lines with *MYC* translocations are also susceptible to growth inhibition by BET inhibitors.

Inhibition of the BET BRD4 protein, thus, proves effective in an in vivo preclinical mode, suggesting that targeting *MYC* expression is feasible in selected cancers (Delmore et al., 2011; Mertz et al., 2011).

The strategy directed toward interrupting Myc-Max dimerization has been forged by several groups (Clausen et al., 2010; Follis et al., 2008, 2009; Hammoudeh et al., 2009; Huang et al., 2006; Mustata et al., 2009; Park et al., 2004; Prochownik and Vogt, 2010). Although proof-of-concept has been documented with inhibitors effective in the micromolar concentration range in vitro, evidence for in vivo effectiveness is still lacking. Nothwithstanding this limitation, the proof-of-concept provided to date suggests that this avenue could be fruitful particularly when new chemistry is applied, such as click-chemistry that bridges two moderate inhibitors against neighboring protein domains of the target to form a more effective inhibitor. Another approach is to consider the unstructured transcriptional regulatory domain and the DNA-binding domain (until it makes contact with DNA) as potential targets for small molecules that would nucleate polypeptide folding and lock the domain in a nonfunctional conformation.

Other strategies have focused on targeting Myc target genes. For example, Myc repression of miR-26a in a Myc-induced liver model of liver cancer has been exploited by treating tumor-bearing animals with adenovirus-associated viral expression of miR-26a (Kota et al., 2009). This strategy results in a remarkable response in this liver cancer model, suggesting that interfering with Myc-regulated miRNAs could be therapeutically feasible (Frenzel et al., 2010; Lovén et al., 2010). Myc target genes such as ornithine decarboxylase (ODC), lactate dehydrogenase A (LDHA), and glutaminase (GLS) have also been targeted by shRNAs or drug-like small molecules in vivo (Figure 3) (Fantin et al., 2006; Le et al., 2010, 2012; Seltzer et al., 2010; Seth et al., 2011; Wang et al., 2010; Xie et al., 2009). These scenarios rely on the necessity of these target genes for the full transforming ability of Myc. It is expected, even with promising preclinical responses to targeting Myc or its target genes, that tumor types and context will add to the complexity and heterogeneity of response to any one strategy. In fact, the avidity of the triple-negative breast cancer subtype for glucose as determined by PET scanning using radiolabeled 18F-deoxyglucose has been linked to a *MYC* gene expression signature, which contains components of glucose fermentation or glycolysis (Palaskas et al., 2011). Thus, targeting metabolism could be strategically aimed at triple-negative breast cancers rather than the estrogen receptor-positive tumors.

Recent screens for synthetic lethality in Myc-transformed cells will also likely provide new therapeutic opportunities such as targeting the death receptor pathway or the use of inhibitors against the aurora- or cyclin-dependent kinases (den Hollander et al., 2010; Yang et al., 2010). A recent synthetic dosage lethality screen uncovered sumoylation of Myc as an essential element for tumor cell growth (Kessler et al., 2012). Further, Myc-induced replicative stress renders transgenic murine lymphomas sensitive to Chk1 inhibitors (Murga et al., 2011). Although synthetic lethality screens are unbiased with respect to the targets, the screens are inherently limited by the choice of tumor cell type. Here, cellular and tissue type context may also affect responses and the spectrum of synthetically lethal targets. In this regard, new therapies targeting Myc, its target genes, or synthetically lethal targets may best be applied in the future together with molecular profiling of cancers for clinical stratification and selection of combination therapies.

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