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An Overview of MYC and Its Interactome

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This review is intended to provide a broad outline of the biological and molecular functions of MYC as well as of the larger protein network within which MYC operates. We present a view of MYC as a sensor that integrates multiple cellular signals to mediate a broad transcriptional response controlling many aspects of cell behavior. We also describe the larger transcriptional network linked to MYC with emphasis on the MXD family of MYC antagonists. Last, we discuss evidence that the network has evolved for millions of years, dating back to the emergence of animals.

A BRIEF HISTORY OF MYC

Retroviral Origins

The history of *MYC* parallels the discovery of other major oncogenes in that it arose from studies on retroviruses associated with animal cancers. The experiments of Ellermann and Bang, and of Rous at the turn of the 20th century, demonstrating that chicken leukemias and sarcomas are transmissible through cell-free filtrates, were largely dismissed by the scientific community (Ellermann and Bang 1908; Rous 1911). Yet over the next 50 years, continuing reports of cell-free tumor transmission, as well as the direct isolation of viruses from tumors, eventually established the principle that many high-incidence animal tumors arise subsequent to viral infection (for a review, see Weiss et al. 1982). During the 1960s and 1970s four distinct retroviruses (MH-2, MC29, CMII, and OK10) were isolated from avian neoplasms and shown to be capable of transforming monocytes/macrophages in vitro, and inducing myelocytomas, endotheliomas, and kidney and liver tumors in chickens (Mladenov et al. 1967; Graf and Beug 1978). The grouping of these four viruses based on their transforming properties turned out to be propitious in that molecular analyses eventually revealed that they possess a common genetic element closely correlated with cell transformation, but not related to virus structural genes nor present in other transforming retroviruses (Sheiness et al. 1978; Bister and Duesberg 1979; Duesberg and Vogt 1979; Hu et al. 1979). Furthermore, deletions within this element crippled the transforming activity of the retrovirus (Ramsay et al. 1980; Bister et al. 1982). This unique viral oncogene was called v-*myc*, for myelocytomatosis (contending names were *mcv* and *mac*), and was shown to be acquired from a highly conserved cellular gene denoted c-*myc* (referred to here as *MYC*) (Roussel et al. 1979; Sheiness and Bishop 1979).

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Association of MYC with Tumorigenesis

The link between *MYC* and cancer was greatly strengthened by the discovery that avian leukosis virus (ALV)-induced B-cell lymphomas consistently contained retroviral insertions in the vicinity of the *MYC* gene (Hayward et al. 1981). Unlike the v-*myc*-containing retroviruses described above, the ALV genome lacks any oncogenic sequences. However in a small subset of ALV integration sites within the host genome, the retroviral enhancer/promoter was found to be inserted proximal to the *MYC* locus, resulting in *MYC* overexpression and deregulation (Fig. 1) (Payne et al. 1982). Therefore, the oncogenic properties of *MYC* are not only manifested by the retroviral-transduced v-*myc* but can also occur as a consequence of viral perturbation of the cellular *MYC* gene. Within the following year it became clear that the cellular *MYC* gene is complicit in neoplasms that lack any retroviral involvement. Consistent chromosomal translocations involving immunoglobulin (Ig) genes had been previously reported in both mineral oil plasmacytomas in mice and in human Burkitt's lymphomas. These translocations were then shown to juxtapose rearranged Ig sequences with non-Ig sequences at the translocation breakpoints, and it was quickly established that the non-Ig sequences originated from a rearranged *MYC* locus (Dalla-Favera et al. 1982a; Shen-Ong et al. 1982; Taub et al. 1982). That *MYC* is crucial for the genesis of B-cell lymphomas was shown through the production of transgenic mice carrying an Ig enhancer linked to *MYC* (Eμ-*MYC* mice) that rapidly develop aggressive B-cell lymphomas with high penetrance (Adams et al. 1985).

The consistent association uncovered in the 1980s between hematopoietic neoplasms and MYC gene alterations owing to retroviruses and chromosomal translocations turned out to only be the tip of the iceberg. *MYC* gene amplification had initially been reported in a myeloid leukemia cell line (Collins and Groudine 1982; Dalla-Favera et al. 1982b) and was soon shown to also occur in colon carcinomas (Alitalo et al. 1983). Moreover, analysis of neuroblastomas, a frequent childhood solid tumor arising from the peripheral nervous system, revealed gene amplifications in a MYC paralog that was designated N-*myc* (herein *MYCN*) (Kohl et al. 1983; Schwab et al. 1983). The amplification of MYCN in neuroblastomas was associated with poor clinical outcome (Brodeur et al. 1984). Another *MYC* family member, L-*myc* (*MYCL1*), was found to be amplified in small cell lung carcinomas (Nau et al. 1985). Therefore all three vertebrate *MYC* family genes (*MYC*, *MYCN*, and *MYCL1*) are linked to the

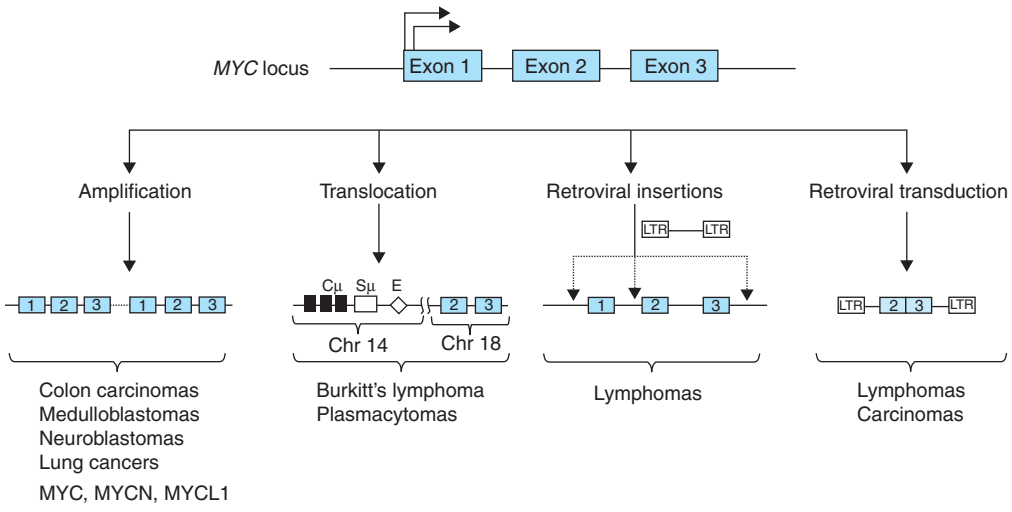

Figure 1. Genetic rearrangements associated with the *MYC* locus in diverse cancers (partial list).

etiology of human cancers. Figure 1 summarizes several modes of *MYC* gene family deregulation.

The initial findings during the 1980s of tumor-related genetic alterations in *MYC* gene family members opened the gates to a veritable flood of further studies that have served to firmly establish an extraordinarily pervasive link between MYC functions and the generation, progression, and maintenance of a wide range of neoplasms (for reviews, see Nesbit et al. 1999; Vita and Henriksson 2006; Beroukhim et al. 2010). Arguably, deregulation of *MYC* family genes underlies the etiology of all cancers. The predominant alterations, such as viral insertional events, chromosomal translocations, and gene amplifications that occur in tumor-associated *MYC* rarely disrupt or mutate its protein-coding sequences (Fig. 1). This is in contrast to many other oncogenes such as Src, Ras, and Abl in which mutations or deletions within autoinhibitory protein domains alleviate inhibition and trigger oncogenic activity. The overarching theme in *MYC* deregulation appears to be events that uncouple *MYC* expression from its normal regulatory constraints, frequently resulting in high levels of MYC expression coupled with an inability to modulate this expression in response to normal cellular and extracellular signals. It is important to note that, in addition to the dramatic cancer-associated rearrangements occurring directly at the *MYC* locus, polymorphisms in DNA sequences distal to *MYC* are known to exert long-range effects on MYC regulation (Wasserman et al. 2010; Wright et al. 2010; Sur et al. 2012; see Cole 2014). Moreover, aberrant MYC expression can result from defects in signal-transduction pathways that activate or repress MYC family gene expression at the transcriptional and posttranscriptional levels (Fig. 2). Among the pathways that heighten MYC expression and are frequently mutated in cancers are Wnt-β-catenin, Sonic hedgehog-Gli, and Notch. For reviews on the role of MYC family genes in neoplasia, see Huang and Weiss (2013), Kuzyk and Mai (2014), Roussel and Robinson (2013), Gabay et al. (2014), and Schmitz et al. (2014). Therapeutic approaches to cancer through inhibition of MYC activity are reviewed in Bradner (2014), Gabay et al. (2014), and Cermelli et al. (2014).

MYC-ENCODED PROTEINS

In 1977, an avian cell line transformed by the v-*myc*-containing retrovirus MC29 was found to produce an unusual viral-related protein of 110,000 kDa (Bister et al. 1977). This protein represented the fusion of a truncated retrovirus core protein precursor with the MYC protein (Mellon et al. 1978; Rettenmier et al. 1979). At the time, all retroviral oncoproteins were known to be localized to the cytoplasm or the plasma membrane. Therefore, it was something of a surprise to find the MC29 virus MYC-containing protein predominantly localized to the cell nucleus (Abrams et al. 1982; Donner et al. 1982; Hann et al. 1983). Later work showed that all cellular MYC family proteins are also nuclear. These early studies suggested MYC to be rather unique among retroviral oncoproteins and pointed to a potentially direct involvement in gene regulation and nuclear function. Subsequently, a large number of distinct oncoproteins were discovered to be localized to the nucleus and, like MYC, involved in transcription (e.g., MYB, FOS, and JUN).

MYC Protein Organization

The overall organization of MYC proteins is similar among MYC paralogs and, to a lesser extent, its orthologs throughout evolution. As diagrammed in Figure 3A for human MYC, the 439 amino acid protein sequence contains several highly conserved regions that are functionally important. These regions are organized in roughly the same way in the MYCN and MYCL1 proteins, whereas many of the sequences outside of the conserved regions are divergent among the three paralogs. In broad terms, MYC proteins can be thought of as possessing (1) a large unstructured amino-terminal region containing the conserved regions known as MYC boxes (MBI, MBII) involved in transcriptional activation; (2) a middle segment rich in proline, glutamic acid, threonine, and proline residues (PEST) as well as two conserved MYC boxes (MBIII and MBIV), and a nuclear localization sequence; and (3) an ~100-amino-acid carboxy-terminal region comprising the basic helix-

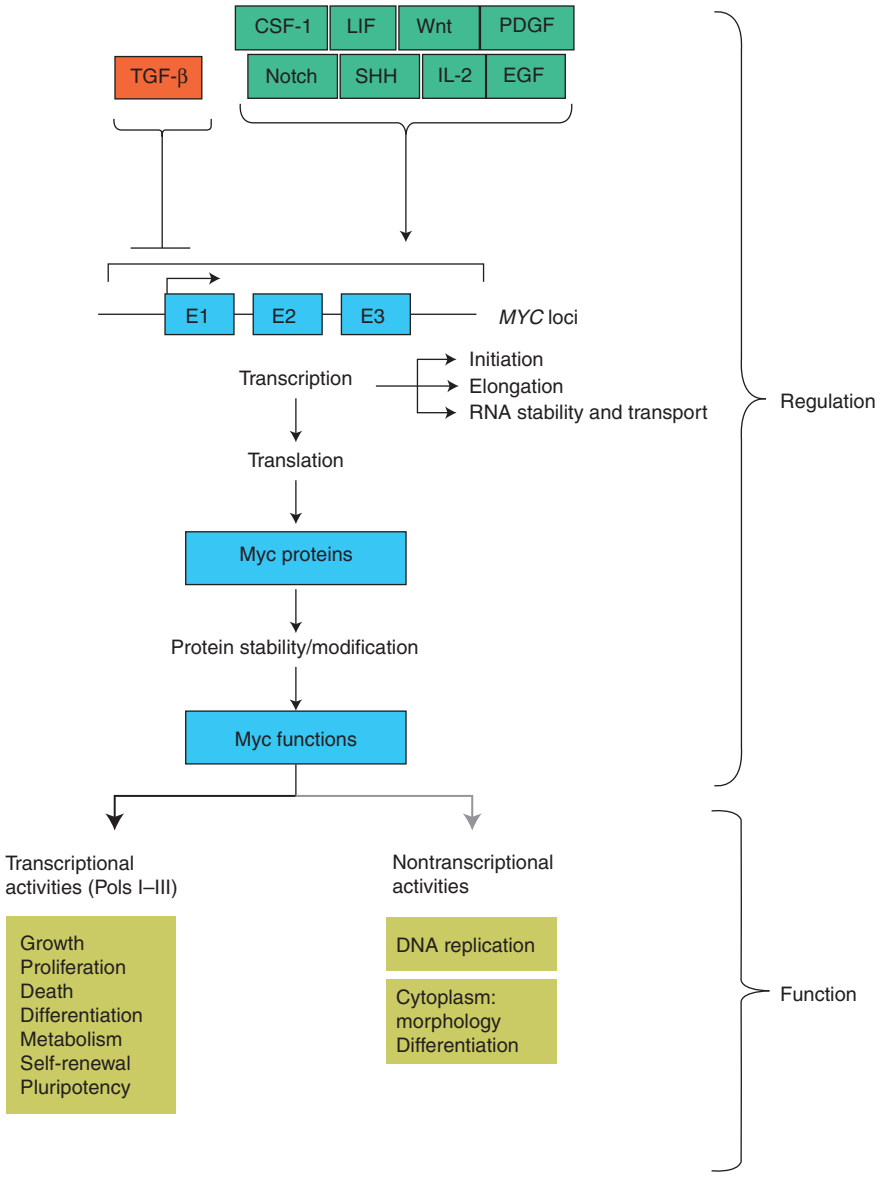

Figure 2. The MYC pathway. Diagrammed is a partial list of environmental signals that lead to changes in MYC expression. The several levels at which MYC, RNA, and MYC protein are known to be regulated are indicated. Cellular readouts related to transcriptional and nontranscriptional activities ascribed to MYC protein are listed.

loop-helix leucine zipper (bHLHZ) domain. MYC family proteins and the other proteins in the extended network (see Fig. 5) form a related subgroup within the much larger class of bHLHZ transcription factors (see below) (Lassar et al. 1989; Murre et al. 1989; Skinner et al. 2010).

MYC Heterodimerization and DNA Binding

Dimerization among proteins of the bHLHZ class is typically mediated through the two HLHZ interfaces, which interact to form a stable four-helix bundle. The resulting dimer specifically binds DNA through formation of induced-

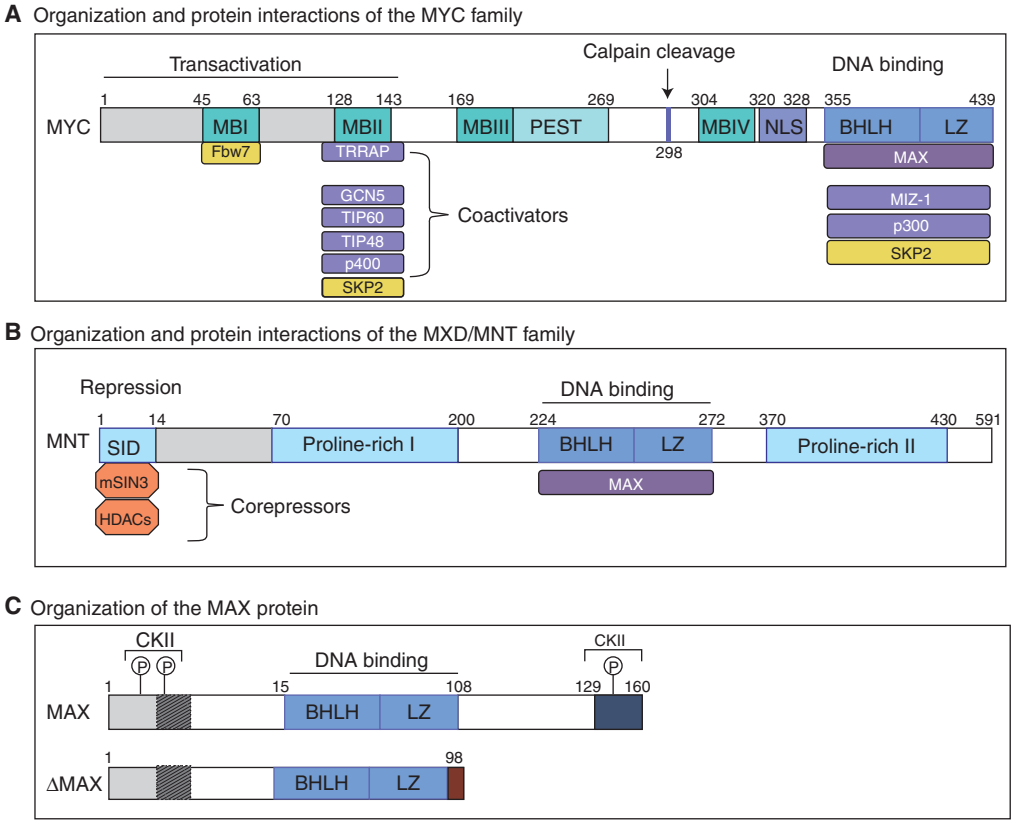

Figure 3. MYC, MNT, and MAX protein organization. Schematic representation of human: (*A*) MYC protein with its major domains and interacting partners. In blue are major functionally characterized transcriptional-binding partners of MYC, and in yellow major E3 ligases involved in MYC turnover. (*B*) MNT, as a representative of MXD family proteins. (*C*) MAX protein. Alternative splicing generates several MAX isoforms. The predominantly expressed MAX proteins (151 and 160 residues in length) differ by a nine-amino-acid segment proximal to the amino terminus (shaded box). In addition, in ΔMAX, the carboxy-terminal 61 amino acids (including the last leucine in the HLHZip) are replaced by five residues before terminating within an alternative exon. Also indicated are casein kinase II (CKII) phosphorylation sites that block Max homodimerization, but not heterodimerization with MYC. MB, MYC boxes; SID, SIN3-interacting domain (see O'Shea and Ayer 2013 for organization of MondoA).

fit helices by the basic regions that straddle the DNA double helix and make specific base contacts within the major groove of DNA (Ferre-D'Amare et al. 1993, 1994). In the case of MYC, homodimerization does not occur under physiological conditions, but a highly specific interaction with the small bHLHZ protein named MAX results in stable heterodimer formation with specific DNA-binding activity (Figs. 3C and 4) (Blackwood and Eisenman 1991; Blackwood et al. 1992; Nair and Burley 2003). Heterodimerization with MAX is essential for MYC association with E-box DNA sequences (5′-CACGTG-3′) and stimulation of transcription at promoter-proximal E boxes (Kretzner et al. 1992; Amati et al. 1993). Furthermore, the MYC–MAX dimeric HLHZ region presents a large solvent-accessible surface area (~1000 Å) forming a platform for binding by other factors, such as Miz-1 and SKP2 (Peukert et al. 1997; Cheng et al. 1999; Nair and Burley 2003; von der Lehr et al. 2003). The structural studies indicate that MYC–MAX bHLHZ dimers can oligomerize to form tetramers (Nair and Burley

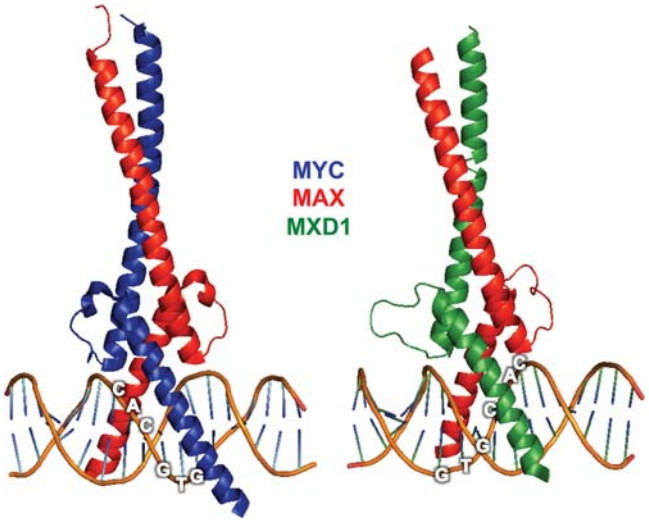

Figure 4. X-ray structures of (*left*) MYC–MAX (PDB: 1NKP), and (*right*) MXD1–MAX (PDB: 1NLW) bHLHZ dimers bound to E-box (5′-CACGTG-3′) DNA sequences at 19-nm and 20-nm resolution, respectively (Nair and Burley 2003). (Image created with the PyMOL Molecular Graphics System, Version 1.5.0.4, Schrödinger, LLC.)

2003) but the physiological relevance of this higher-order form has not been unambiguously validated (Walhout et al. 1997; Vervoorts and Luscher 1999; Lebel et al. 2007).

MAX also homodimerizes, albeit weakly, relative to its heterodimerization with MYC. Moreover phosphorylation of MAX, while not interfering with its heterodimerization with MYC, inhibits MAX homodimerization in vivo (Berberich and Cole 1992), a finding consistent with the result that enforced MAX expression blocks MYC biological activity, probably through competition for E-box-binding sites (Lindeman et al. 1995; Canelles et al. 1997). Several alternatively spliced forms of MAX are expressed, one of which, ΔMAX, lacks the 62-residue carboxy-terminal region but retains the entire bHLHZ except for the last leucine of the Zipper (Fig. 3C) (Blackwood and Eisenman 1991; Makela et al. 1992). Induction of an alternative splicing factor, following activating EGFR mutation in glioblastoma, generates ΔMAX, which dimerizes with MYC and augments MYC-transforming activity (Makela et al. 1992; Babic et al. 2013). The mechanism underlying the elevated MYC activity is unknown but we surmise that the carboxyl terminus of MAX normally permits association of a negative regulatory factor with the heterodimer.

Although many biological functions of MYC family proteins appear to be dependent on their interaction with MAX, there is considerable evidence for MAX-independent activities of MYC (Hopewell and Ziff 1995; Steiger et al. 2008; Gallant 2013). Furthermore, MYC proteins, with or without MAX, can be detected at non-E-box DNA sequences through interaction with other DNA-binding proteins including NF-Y, and subunits of RNA polymerase III (Izumi et al. 2001; Gomez-Roman et al. 2003; Steiger et al. 2008; Sabò and Amati 2014). Perhaps such MAX-independent activities of MYC are the basis for the connection between MAX loss-of-function mutations and human pheochromocytomas (Comino-Mendez et al. 2011).

MYC Box Functions

Of the highly conserved MYC box regions within MYC family proteins, MBI and MBII are the best characterized (Fig. 3A). MBI serves as a phosphodegron and is involved in the ubiquitylation and proteasomal degradation of MYC. MYC proteins are very unstable with half-lives

of 20–30 min in many normal cells (Hann and Eisenman 1984). However, the exact half-lives of MYC family proteins are dependent on physiological context, and, in many tumors, stabilization of MYC contributes to its deregulation (Salghetti et al. 1999; Gregory and Hann 2000; Sears et al. 2000; Cartwright et al. 2005). Multiple ubiquitin ligases have recently been shown to control MYC stability (see Farrell and Sears 2014). One of these ubiquitin ligases, FBW7, regulates MYC and MYCN stability in response to phosphorylation of Serine 62 and Threonine 58 within MBI (Welcker et al. 2004a,b; Yada et al. 2004). Interestingly many human B-cell lymphomas contain point mutations in MBI that block FBW7 binding and augment MYC stability (Bahram et al. 2000). MBI mutations have been shown to increase oncogenicity in several tumor models (Hemann et al. 2005; Wang et al. 2011b; B Freie and RN Eisenman, unpubl.). Conversely, tumorigenic phenotypes associated with Fbw7 mutations have been linked, for example in lymphoid and myeloid leukemias, to increased MYC protein stability. However, this ligase has many regulatory proteins as substrates and it is unclear to what extent they also contribute to Fbw7 oncogenicity (Welcker and Clurman 2008; King et al. 2013).

MBII, the most studied region within the MYC transactivation domain (TAD), functions as a hub for binding to multiple key interactors including components of histone acetyltransferase (HAT) complexes such as TRAPP-GCN5, Tip60, and Tip48 (McMahon et al. 1998) to promote histone acetylation and gene activation. MBII is important for most known MYC activities (Stone et al. 1987). Moreover, MBII is involved in MYC protein turnover because it is a docking site for SKP2, one of several E3 ligases, in addition to Fbw7, involved in the degradation of MYC (Kim et al. 2003; von der Lehr et al. 2003) (see Farrell and Sears 2014 for a detailed discussion of mechanisms underlying MYC degradation).

The MBI-MBII TAD region is also involved in association with other effectors of MYC activity such as the bromodomain protein BRD4 and the P-TEFb (cyclin T1, CDK9) transcriptional pause-release complex (Eberhardy and Farnham 2002; Kanazawa et al. 2003; Gargano et al. 2007; Wu et al. 2013; Rahl and Young 2014). In addition to MBI and MBII, there are conserved sequences within the central regions of MYC that are considered to be functionally important (Fig. 3). These include a nuclear localization signal (NLS), as well as MBIII and MBIV implicated in MYC cellular-transforming activity, transcription, and apoptosis (Herbst et al. 2004, 2005; Cowling et al. 2006).

MYC as a Sensor and Effector of Cellular Information

MYC normally functions as a sensor, integrating multiple cellular signals and mediating a transcriptional response that drives cell growth and proliferation and impacts differentiation, survival, and pluripotency. This concept of MYC function derives from extensive research relating to, first, how the abundance of the MYC protein is controlled, and second, the molecular functions of the MYC protein (outlined in Fig. 2) (see Levens 2013). Control of *MYC* gene expression and the production and fate of MYC protein occurs at nearly every level known to molecular biology. As mentioned above, activation of MYC transcription is an end point for a broad range of signal-transduction pathways. Transcription factors harnessed by these pathways bind to the *MYC* promoter to regulate transcription initiation and elongation, dependent on cellular context and chromatin conformation (Liu and Levens 2006; Wierstra and Alves 2008). Other factors appear to control *MYC* mRNA stability, export, and translation. At the level of the MYC protein, further regulation is exerted through posttranslational modification (Hann 2006) as well as multiple ubiquitin ligases, which together act as arbiters of MYC stability (see Farrell and Sears 2014). Simply put, MYC is under extraordinarily tight regulation by the cell. A corollary of this is that defects in regulation can, and do, occur at many levels, leading to the increased abundance and inappropriate expression of MYC typical of many cancers (see Huang and Weiss 2013; Roussel and Robinson 2013; Gabay et al. 2014; Schmitz et al. 2014). Our increasing knowledge

of key regulatory events has led, and will continue to lead, to therapeutic approaches aimed at subverting MYC production (Gustafson and Weiss 2010; Dawson et al. 2011; Delmore et al. 2011; Mertz et al. 2011; Zuber et al. 2011; Loven et al. 2013; Puissant et al. 2013; Bradner 2014).

Once formed, MYC proteins function predominantly in transcriptional regulation. Nonetheless, MYC transcriptional activity in standard reporter assays is considerably weaker than many other well-studied transcription factors. Initial studies focused on identifying what were expected to be a small number of MYC–MAX regulated genes. Over time, the number of these MYC "target genes" continued to grow awkwardly large. Although most targets are activated, a substantial fraction were shown to be repressed by MYC. Eventually, application of methods to detect sequences directly bound by MYC in mammalian and *Drosophila* cells led to identification of >15% of genomic loci as MYC targets (Fernandez et al. 2003; Orian et al. 2003). A disproportionate number of bound genes appear to be involved in cell growth (i.e., translation, ribosome biogenesis, and metabolic processes) (Zeller et al. 2006). This fit well with microarray expression profiling studies, with genetic analyses, and with other work showing that MYC, in addition to regulating RNA polymerase II transcribed genes, is directly involved in RNA polymerase I and RNA polymerase III transcription (see Campbell and White 2014). Several classes of microRNAs were also found to be regulated by MYC (see Psathas and Thomas-Tikhonenko 2014). The notion emerged of a MYC "signature" encompassing groups of target genes devoted to growth and pluripotency (Kim et al. 2010; Ji et al. 2011). Analysis of target genes indicates that MYC binding results in hyperacetylation of histones, consistent with MYC's recruitment of HATs (Martinato et al. 2008). However MYC–MAX interacts with a bewildering variety of other factors with diverse activities (chromatin remodelers, demethylases, antipausing factors, as well as other transcription factors such as MIZ-1 and the estrogen receptor) (see Hann 2014). One implication of this is that MYC's precise molecular function in transcriptional activation and repression may be dependent on the particular factors recruited by MYC, the constellation of other transcription factors proximal to the binding site, and the chromatin context of the target gene (Cheng et al. 2006; Guccione et al. 2006; Eilers and Eisenman 2008).

Recent studies have challenged this polyfunctional view of MYC, as well as the concept of a restricted MYC signature. This work provides evidence that MYC is bound at every active gene in a given cell type and functions to increase transcription at these loci by recruitment of a complex that abrogates transcriptional pausing downstream from the transcription start site (TSS) and thereby promotes transcriptional elongation (Rahl et al. 2010; Lin et al. 2012; Nie et al. 2012). In this view, MYC acts solely as an amplifier of ongoing gene expression, and the apparent repression of target genes is owing to the normalization procedure used or to events occurring as an indirect or secondary response to MYC's stimulation of elongation (Loven et al. 2012). Not surprisingly, this readjusted concept of MYC function has evoked considerable debate (see Levens 2013; Wiese et al. 2013; Rahl and Young 2014; Sabò and Amati 2014). Many other reviews in the literature examine MYC biological function in the light of these contrasting views.

Although MYC clearly has a major function in transcriptional regulation it is important to note that several distinct nontranscriptional activities of MYC have been reported. MYC was found to directly promote DNA replication by recruiting licensing factors to origins of replication and collaborating with the Werner DNA helicase to accelerate S-phase entry (Dominguez-Sola et al. 2007; Robinson et al. 2009; Dominguez-Sola and Gautier 2014). Another nontranscriptional activity of MYC derives from the cleavage of full-length MYC protein by calpain protease to remove the NLS and the entire bHLHZ domain (Fig. 3A). MYC-Nick, the resulting large amino-terminal segment of MYC, is predominantly cytoplasmic and influences cell morphology, differentiation, and survival at least in part through acetyltransferases bound to MBII (Conacci-Sorrell et al. 2010; M Conacci-Sorrell and RN Eisenman, unpubl.).

BEYOND MYC: THE EXTENDED MAX–MLX NETWORK

The heterodimeric interactions between the bHLHZ domains of MYC family proteins and MAX are striking in terms of both their specificity and evolutionary conservation (Blackwood and Eisenman 1991; Gallant et al. 1996; Nair and Burley 2003) (and see below). However, although MYC does not participate in dimerization with bHLHZ proteins other than MAX, there is considerable evidence that MAX dimerizes with another group of bHLHZ proteins: the MXD family and MGA. Moreover, a MAX-like bHLHZ protein known as MLX, specifically heterodimerizes with MondoA (MLXIP) and ChREBP (MondoB or MLXIPL) as well as with a subset of MXD family proteins. Taken together, the multiple interactions of MAX and MLX appear to constitute an extended network through which MYC, MXD, and Mondo gene families mediate a broad transcriptional response to mitogenic, growth arrest, and metabolic signals (diagrammed in Fig. 5) (see O'Shea and Ayer 2013).

The MXD Protein Family: Antagonists and Enablers of MYC Function

The MXD (originally called MAD) proteins were initially identified in protein interaction screens aimed at discovering novel dimerization partners for MAX (Ayer et al. 1993; Zervos et al. 1993). This family of bHLHZ proteins comprises MXD1–MXD4 and the more distantly related MNT (Hurlin et al. 1995b, 1997; Meroni et al. 1997). In addition, MAX binds to MGA, the largest protein in the MAX network and perhaps the most unusual in that it possesses both T-domain and bHLHZ DNA-binding motifs (Hurlin et al. 1999).

MXD Proteins Interact with the mSin3 Corepressor

In several respects the MXD proteins mirror the MYC family in that they do not homodimerize or bind DNA as monomers, whereas as heterodimers with MAX they specifically bind E-box sequences (Fig. 4). However, unlike MYC–MAX, which generally stimulates transcription,

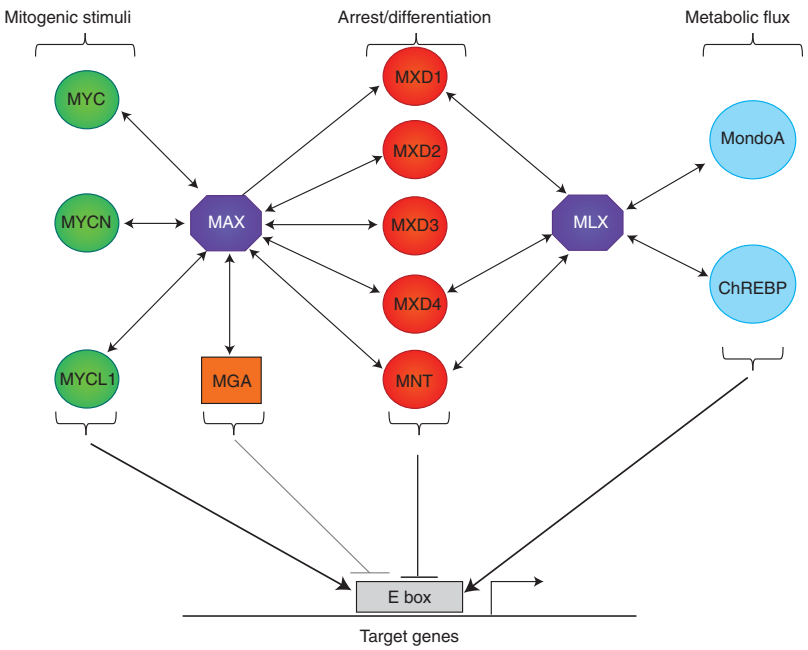

Figure 5. Diagram of the extended MAX–MLX network. Double-headed arrows indicate individual interactions between network components.

the binding of MXD–MAX heterodimers to promoter-proximal E boxes results in transcriptional repression. The transcriptional repression activity of MXD proteins is derived from their ability to bind the large corepressor complex known as mSIN3 (Ayer et al. 1995; Hurlin et al. 1995b; Schreiber-Agus et al. 1995; Hurlin et al. 1997). All MXD family proteins possess a conserved amino acid sequence (the mSin3 interaction domain, SID) near their amino termini that directly interacts with one of four paired amphipathic α-helical (PAH) domains within mSIN3 (Fig. 3B). The solution structure of the mSin3-PAH2:MXD1-SID interface has been solved and has provided a model for the specificity of this critical interaction (Brubaker et al. 2000; Cowley et al. 2004). There is some evidence that this interaction is regulated. For example, in the case of MNT, phosphorylation through the ERK pathway has been reported to block its association with mSIN3 (Popov et al. 2005).

mSIN3 acts as a scaffold that interacts with numerous factors, including class I histone deacetylases (HDAC1 and HDAC2), whose ability to deacetylate histones H3 and H4 in active chromatin is frequently associated with transcriptional silencing (Hassig et al. 1997; Laherty et al. 1997; Zhang et al. 1997). The functions of other proteins recruited by the mSin3 corepressor complex are less clear, but several of these have also been linked to repression and may further regulate the activities of the MXD family (Alland et al. 1997; Heinzel et al. 1997; Nomura et al. 1999; Shiio et al. 2006).

Antagonism between MYC and MXD

Recruitment of the Sin3-HDAC corepressor by the MXD family contrasts with MYC's association with the TRRAP-GCN5 coactivator, and other HATs, and suggests that MYC and MXD possess opposing functions. In principle, MYC and MXD may act as antagonists at three levels: (1) competition for available MAX to form heterodimers, (2) competition between heterodimers for E-box-binding sites, and (3) activation versus repression at bound genes. There is considerable biological evidence from overexpression studies that MYC and MXD family proteins are functionally antagonistic. Overexpression of MYC drives growth and proliferation in a wide range of cell types, whereas enforced expression of MXD family members generally arrests growth and proliferation in normal and MYC-transformed cells (Lahoz et al. 1994; Chen et al. 1995; Hurlin et al. 1995b, 1997; Koskinen et al. 1995; Roussel et al. 1996; Iritani et al. 2002; Marcotte et al. 2003). Murine lymphoid cells provide a good example of the opposing effects of MYC and MXD on growth. In primary T cells, MYC is required for the growth and proliferation of immature thymocytes and for antigenic activation (Dose et al. 2006; Wang et al. 2011a). These events are significantly inhibited by ectopic MXD1 expression, as is the expression of a large number of MYC-induced growth-related genes (Iritani et al. 2002). Moreover, overexpression of the sole *Drosophila* MXD ortholog dMnt inhibits the growth and proliferation of cells in the wing-imaginal disc, functions known to be linked to dMyc activity (Johnston et al. 1999; Loo et al. 2005; Gallant 2013). To date there has been only limited analysis of genomic-binding sites occupied by MXD proteins; however, in both *Drosophila* and vertebrate cells there appears to be considerable overlap between MYC and MNT sites (Orian et al. 2003; Toyo-oka et al. 2006). Therefore, MXD proteins, at least when overexpressed, appear to possess the capacity to block MYC activity at shared binding sites. It will be interesting to determine whether, and how, MXD antagonism is exerted on MYC's activity as a transcriptional amplifier.

Regulation of MYC and MXD Expression

An interesting issue is how the apparent antagonism between MYC and MXD is manifested during normal and tumor cell growth. Importantly, the expression patterns of MYC and the different MXD family members are dependent on cell cycle and differentiation status (Queva et al. 1998) (for a summary, see a review by Hooker and Hurlin 2006). Although MYC levels are nearly undetectable during quiescence, MYC RNA and proteins are rapidly induced upon cell-cycle entry and remain relatively constant during cell-cycle progression (Kelly et al. 1983;

Hann et al. 1985). In contrast, MXD1, 2, and 4 are present in resting cells and decrease upon mitogen-induced cell-cycle entry, when MYC is induced. Importantly, MYC is down-regulated in many cell types during terminal differentiation, a time during which MXD1, 2, and 4 proteins are expressed. Thus, MYC is largely associated with proliferation, whereas MXD1, 2, and 4 expression is characteristic of nonproliferating cells consistent with findings from the overexpression studies mentioned above (e.g., Lahoz et al. 1994; Hurlin et al. 1995a; Iritani et al. 2002). MXD3 and MNT are interesting exceptions to this inverse pattern of MYC and MXD expression in that they are both expressed during cell proliferation. MNT is present, coincident with MYC, throughout the cell cycle and persists following differentiation, whereas MXD3 expression is restricted to cells in S phase (Queva et al. 2001; Yun et al. 2007).

Differentiation

Induction of MXD1 occurs during terminal differentiation in a wide range of cell types including myeloid, muscle, epidermal, and neuronal cells (Ayer and Eisenman 1993; Larsson et al. 1994; Hurlin et al. 1995a; Queva et al. 1998; Loo et al. 2005). During the transition from proliferation to differentiation, MYC–MAX heterodimers are replaced by MXD1–MAX complexes (Ayer and Eisenman 1993; Hurlin et al. 1995a; Xu et al. 2001). Because both heterodimer pairs specifically bind E-box DNA sequences, it has been surmised that the heterodimer switch during differentiation results in a switch from activation to repression of MYC target genes, an idea supported by findings of decreased histone acetylation and down-regulation of gene expression at several gene promoters known to be regulated by MYC (Bouchard et al. 2001; Xu et al. 2001; Iritani et al. 2002). However, as a systematic study of MXD family binding to genomic DNA has not yet been performed, the full extent to which the widespread stimulation of gene expression mediated by MYC is actually suppressed by MXD1 (or the other MXD family members) during differentiation remains to be determined.

Genetic deletion studies support the view that MXD1 and MXD2 restrain MYC activity. Targeted deletion of *MXD1* in mice produced a surprisingly mild phenotype. Overall embryonic and adult development was normal but an increased frequency of immature granulocyte progenitors was apparent (Foley et al. 1998). This was owing to impaired cell-cycle exit of granulocytic precursors resulting in delayed onset of terminal differentiation. The precursors were additionally found to be more sensitive to apoptosis induced upon cytokine removal, enabling the mice to retain nearly normal levels of mature granulocytes. Mice with *MXD2* (originally called *Mxi1*) deletions also developed normally but displayed a hyperplastic phenotype in multiple tissues and ectopic proliferation within several organs as well as a marked sensitivity to neoplasia following chemical carcinogen treatment (Schreiber-Agus et al. 1998; for a review, see Foley and Eisenman 1999). MXD3 null mice are phenotypically normal, although several tissues show an enhanced sensitivity to apoptotic stimuli (Queva et al. 2001). The relatively minor effects of the MXD1 and MXD2 single gene deletions on embryogenesis may be owing to the fact that they are normally expressed during a period (i.e., differentiation) when MYC is strongly down-regulated. Therefore, they may not directly oppose MYC activity but rather function along with other differentiation factors to repress growth and proliferation genes that are stimulated by MYC before differentiation. In contrast, constitutive deletion of MNT, which is induced by mitogenic stimuli and coexpressed with MYC, results in early postnatal lethality (Toyo-oka et al. 2004; Link et al. 2012). Redundancy among MXD paralogs may also contribute to the mild phenotypes of the single-gene MXD1–4 knockouts. However, null mutation of the single MXD ortholog in *Drosophila* also displayed only a modest effect on growth (Loo et al. 2005) suggesting redundancy cannot fully explain the mild single knockout phenotypes.

Oncogenesis

Because deregulated MYC is fundamental to the establishment and maintenance of many

tumor types, it seemed likely that MXD family members could act as tumor suppressors by antagonizing MYC function. Perhaps the most likely contender for tumor suppression activity is MXD2, as its constitutive deletion in mice results in widespread hyperplasia and a tumor-prone phenotype (Schreiber-Agus et al. 1998). *MXD2* is located on human chromosome 10q24, a region deleted in a broad spectrum of human tumors and that also contains the PTEN tumor suppressor. Loss of heterozygosity in the MXD2 region, and potentially inactivating mutations in the remaining MXD2 allele, were reported in a subpopulation of prostate cancer cells (Eagle et al. 1995; Prochownik et al. 1998). However, a series of extensive follow-up studies were unable to corroborate these findings (Bartsch et al. 1996; Edwards et al. 1997; Kuczyk et al. 1998). To date there is no compelling evidence that MXD1–4 act as tumor suppressors. Perhaps the loss of MXD proteins that are normally expressed during arrest and differentiation is simply irrelevant in the context of the high levels of deregulated MYC that drive tumor initiation. This may not be the case for MGA and MNT, which appear to act as tumor suppressors.

Potentially inactivating mutations in MGA have been recurrently detected in chronic lymphocytic leukemia (Edelmann et al. 2012; De Paoli et al. 2013) and recent studies on MNT show that it functions as both an antagonist and enabler of MYC's oncogenic activities. There have been few studies on MGA, but it has been found associated with two different repression complexes (Ogawa et al. 2002; Tahiliani et al. 2007), and in zebrafish the MGA ortholog regulates bmp2b/swirl during gastrulation (ST Dougan, pers. comm.). MNT, as mentioned above, is generally coexpressed with MYC in proliferating cells and *MNT* null mice display developmental defects and die soon after birth (Toyo-oka et al. 2004). Murine embryonic fibroblasts (MEFs) derived from these mice, or in which MNT has been depleted, resemble cells with activated MYC in that they show marked increases in proliferation rate, enhanced expression of known MYC-regulated genes, and are prone to apoptosis (Hurlin et al. 2003; Nilsson et al. 2004). Mice with conditional *MNT* deletions in mammary epithelium or T cells show hyperproliferation of these cell types and frequently develop mammary adenocarcinomas and T-cell lymphomas, respectively, late in life (Dezfouli et al. 2006; Toyo-oka et al. 2006). Additionally, in metastatic tumor cells under hypoxic conditions, hypoxia-inducible factors (HIF-1α and HIF-2α) induce a microRNA (miR-210), resulting in MNT down-regulation and an MYC-dependent bypass of cell-cycle arrest (Zhang et al. 2009).

The data described above are consistent with the notion that MNT opposes MYC function. Yet that antagonism acts to favor MYC-induced tumorigenesis because the dominant physiological activity of MNT is to oppose the proapoptotic activity elicited by MYC (Link et al. 2012). In biological settings where MYC protein levels are elevated, cell survival becomes increasingly dependent on MNT as shown by the fact that even a small increase in MYC abundance compromises cell survival in the absence of MNT. The lowered threshold for MYC-induced apoptosis caused by loss of MNT is tied to the aberrant accumulation of reactive oxygen species (ROS) (Link et al. 2012). Therefore, as proposed for MYC-induced neoplasia (Vafa et al. 2002), tumors generated as a consequence of MNT deletion may arise owing to ROS-induced oxidative damage to DNA and mutations that suppress apoptosis (see Kuzyk and Mai 2014). These studies suggest that although MNT can antagonize both MYC-stimulated proliferation and apoptosis, its prosurvival function is critical for MYC-driven tumorigenesis. Comprehensive analysis of genomic binding by MYC and MXD family proteins will be required to more fully understand the functional relationships among these transcription factors.

Expanding the Network: MLX and Its Dimerization Partners

MLX is a MAX-like bHLHZ class protein initially discovered as a dimerization partner for a subset of MXD family proteins, namely, MXD1, MXD4, and MNT (Billin et al. 1999; Meroni et al. 2000). MXD–MLX heterodimers interact

with mSIN3, bind E-box DNA sequences, and repress transcription, apparently acting similarly to MXD–MAX dimers. MLX does not appear to associate with MAX or MYC family proteins; however, further analysis revealed two other MLX dimerization partners: MondoA and ChREBP (Fig. 5) (Billin et al. 2000). Both MondoA and ChREBP are cytoplasmic-nuclear shuttling proteins whose nuclear accumulation is triggered by glucose-derived metabolites (Stoltzman et al. 2008; Peterson et al. 2010). MondoA-MLX and ChREBP-MLX dimers bind E-box sequences and regulate genes involved in glucose and glutamine metabolism, processes important for the biology of normal and cancer cells. Therefore, MondoA and ChREBP heterodimers with MLX act as nutrient-sensing transcription factors, and there is considerable evidence indicating that they are critical regulators of cell metabolism. For a detailed discussion of these proteins and their functions see O'Shea and Ayer (2013).

Implications of an Extended MYC Network

The existence of an extended MYC network (Fig. 5) has potentially important implications for understanding MYC functions, the most obvious of which is that MYC does not act alone but within the context of a larger protein interactome. It is also predicted that changes in the abundance of individual network components will have an impact on the activity of all of the network factors through competition for available MAX and MLX as well as for DNA-binding sites. Although initial studies suggested that MAX, a highly stable protein, is present in excess relative to MYC (Blackwood et al. 1992), more recent work indicates that, at least in some biological settings, MYC and MNT compete for binding to limiting amounts of MAX (Walker et al. 2005). MAX availability is further modulated by the turnover of MXD family proteins, which are regulated through ubiquitin-mediated proteasomal degradation and display short half-lives (Zhu et al. 2008). In contrast, MondoA and ChREBP are stable proteins and tight regulation of their transcriptional activity occurs through their nuclear accumulation in response to changes in metabolic flux (see O'Shea and Ayer 2013). Moreover, not all network members are equal when it comes to dimerization with MAX. A live cell bimolecular fluorescence complementation analysis reported different apparent binding affinities for MAX among MXD proteins compared with MYC and differences in subnuclear localization patterns between MYC–MAX and MXD–MAX heterodimers (Grinberg et al. 2004). Although the consequences of these differences in binding and localization are unknown, variation in binding efficiencies are nonetheless compatible with the idea that modulations in the levels of individual family members may have distinct effects on network activity. The possibility that even relatively small changes in the abundance of individual factors may have network-wide consequences perhaps accounts in part for the extraordinary degree of regulation of MYC expression shown at transcriptional, posttranscriptional, and posttranslational levels (Fig. 2) (see Levens 2013; Farrell and Sears 2014).

There is also evidence for regulatory cross talk among network members. To begin with, it has long been known that MYC negatively autoregulates its own expression. This appears to occur through an evolutionarily conserved circuitry involving the Polycomb complex that can be abrogated during tumorigenesis (Grignani et al. 1990; Penn et al. 1990; Goodliffe et al. 2005; Kaur and Cole 2013). Cross-regulation may also extend to other MYC family members as well as other network components (Rosenbaum et al. 1989). MYC, complexed with MIZ-1, has been shown to repress MXD4 in erythroleukemia cells (Kime and Wright 2003). MYC also appears to up-regulate MondoA and ChREBP, factors that in turn influence MYC-driven metabolic reprogramming during tumor progression (Lin et al. 2009; Kaadige et al. 2010; Sloan and Ayer 2010; P Carroll, D Diolaiti, L McFerrin et al., unpubl.). Increased abundance of MondoA and ChREBP would be expected to sequester MLX, potentially blocking the formation of MXD–MLX dimers. At present, there is no information as to whether MXD–MLX and MXD–MAX heterodimers differ functionally.

However, recruitment of MLX into MondoA and ChREBP heterodimers would likely increase competition between MYC and coexpressed MXD proteins for available MAX. Perhaps it is an imbalance in the network that is responsible for the hereditary pheochromocytomas that arise in association with inactivating mutations in MAX (Comino-Mendez et al. 2011). We are clearly still at an early stage in understanding the ramifications of network function. We expect that genetic studies involving alterations in the levels of network members combined with chromatin immunoprecipitation analyses of heterodimer binding to DNA will be required to understand the dynamics of the integrated MYC network in greater detail.

EVOLUTION OF A METAZOAN GENE NETWORK

The MAX and MLX networks have been primarily characterized in mice, humans, and *Drosophila*. Annotation of these proteins indicates that network orthologs have overlapping functions (e.g., mammalian MYC regulates growth and proliferation, whereas *Drosophila* dMyc predominantly drives growth) (for reviews, see Brown et al. 2008; Bellosta and Gallant 2010; Gallant 2013). Despite this functional overlap, these species differ considerably in complexity and number of members in the extended network. A survey of the animal kingdom reveals these networks all radiated from a common core set of proteins that emerged before animal divergence (Fig. 6) (McFerrin and Atchley 2011). Strikingly, MAX and MLX network members span all known Metazoan lineages, emphasizing the importance of these ancient transcription factors.

The origin of the MAX and MLX networks dates to over 500 million years ago, with the protein and DNA interactions of these transcription factors predating the origin of animals. In the choanoflagellate *Monosiga brevicollis*, an ancestor of animals that can grow as a uni- or multicellular organism, MYC and MAX heterodimerize, localize to the nucleus, and bind E boxes (Young et al. 2011). MYC and MAX similarly heterodimerize and target E boxes in the early diploblastic cnidarian *Hydra*, where Myc shows oncogenic potential and is specifically activated in all proliferating cell types (Hartl et al. 2010). MAX, MYC, MXD, MLX, and Mondo sequences have also been identified in the Placazoan *Trichoplax adhaerens*, considered the simplest animal with the smallest known genome.

Network Divergence

Within the animal kingdom, lineage-specific radiation and deletion of MAX and MLX network components (based on conservation of bHLHZ domains) gives rise to four main network configurations: Core, Diptera, Nematode, and Vertebrate (numbered 1–4 in Fig. 6). The core network, consisting of MYC, MAX, MNT, MXD, MLX, and Mondo proteins, is the basis from which other animal networks evolved. Nematodes show extensive divergence, presumably owing to a massive gene reduction and rearrangement (Witherspoon and Robertson 2003; Denver et al. 2004; Coghlan 2005), and contain two MAX orthologs (Mxl-1 and Mxl-3), a single MLX ortholog (Mxl-2), a MXD-like protein (MDL-1), and a MYC and Mondo-like protein (MML-1). Mxl-1 and Mxl-3 apparently heterodimerize with MDL-1, whereas Mxl-2 binds MML-1 (Yuan et al. 1998; Gallant 2006; Pickett et al. 2007). Hence, the MLX network is conserved in nematodes, but it is not known if the antagonistic transcriptional regulation characteristic of MYC and MNT is performed by MDL-1 and MML-1.

The Diptera lineage, including fruit flies and mosquitoes, possesses a minimal network in that these organisms contain single orthologs of MYC, MAX, MNT, MLX, and Mondo (Mio) (Gallant et al. 1996; Peyrefitte et al. 2001; Loo et al. 2005; Billin and Ayer 2006). A *Drosophila* mutation originally designated *diminutive* (*dm*), resulting in abnormally small body size and female sterility (Bridges 1935), was later shown to correspond to the locus encoding the MYC ortholog (Gallant et al. 1996; Schreiber-Agus et al. 1997). Extensive studies in *Drosophila* have shown that dMyc is closely linked to multiple signaling pathways and acts as an essential regulator of growth, prolifera-

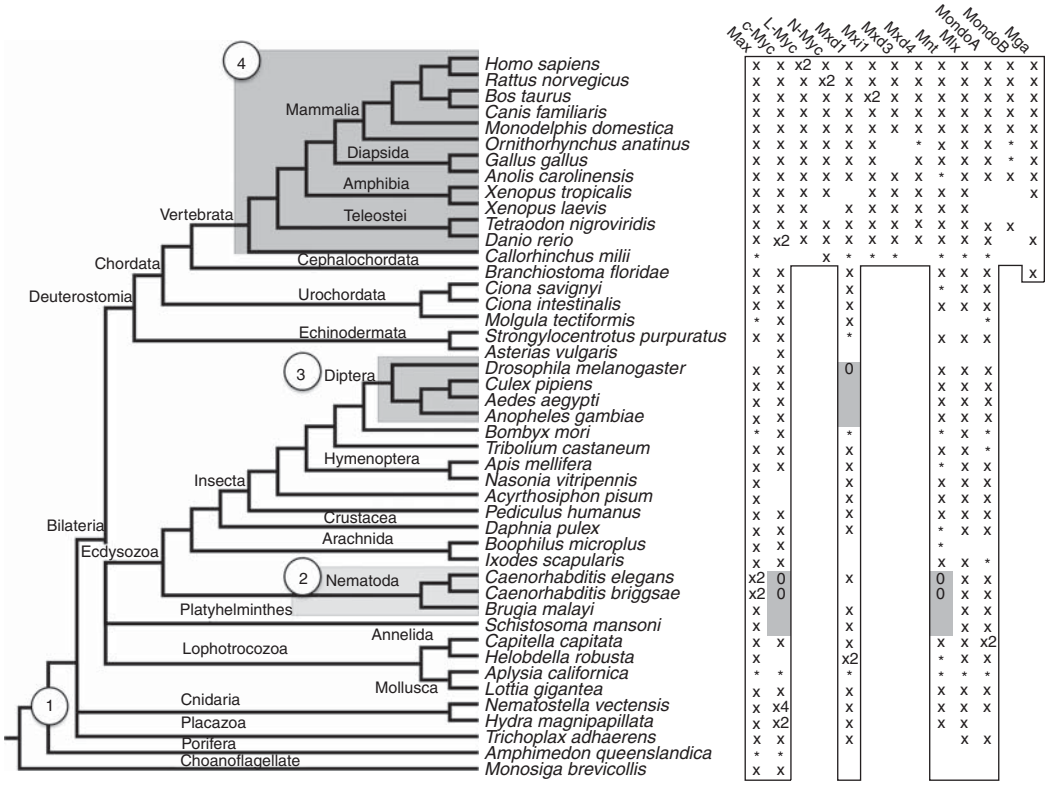

Figure 6. MAX and MLX network protein distribution based on conservation of bHLHZ domains. (*Left*) Species tree representing organism divergence. Circled numbers correspond to the emergence of the four major networks. (*Right*) Outlined and gray cells indicate proteins that are expected to be present or absent, respectively, through identifiable conservation of the homologous bHLHZ domain. "X" and "*", respectively, indicate the full or partial bHLHZ sequence was found, whereas "0" marks where the protein is known to be absent. Note the species tree is based on the relationship among species listed and is not derived from the network proteins listed on the *right*.

tion, and apoptosis, whereas dMnt antagonizes dMyc to negatively regulate cell growth and body size (Johnston et al. 1999; Loo et al. 2005; Bellosta and Gallant 2010; Gallant 2013; Johnston 2014). Furthermore, a homologous ubiquitin ligase system in flies and mammals regulates dMyc abundance in response to phosphorylation of a conserved degron similar to vertebrate MBI (Moberg et al. 2004; Welcker et al. 2004b; Yada et al. 2004; Galletti et al. 2009). dMlx and its MondoA/ChREBP-like dimerization partner Mio have been identified in *Drosophila* and recently shown to regulate sugar sensing and utilization (Havula et al. 2013; Musselman et al. 2013). The existence of this pared-down MAX–MLX network in *Drosophila* will continue to provide an excellent model for dissecting basic network functions (see Gallant 2013; Johnston 2014).

In contrast, two whole genome duplication (WGD) events, occurring either before or during vertebrate divergence (Dehal and Boore 2005), formed the MYC (MYC, MYCN, MYCL1), MXD (MXD1–4, MNT), and Mondo (MondoA, MondoB/ChREBP) protein families. Only a single copy of MAX and MLX exists in vertebrates despite multiple duplication events, suggesting that the regulation of these proteins is highly controlled by natural selection. Another MAX network member, MGA, also arose during vertebrate divergence and is predicted to be a fourth MYC family member because of its bHLHZ domain similarity (Hurlin et al. 1999; McFerrin and Atchley 2011). In

addition, MYC has experienced subsequent and independent duplication events. Old world primates, but not prosimians, show a duplication of MYCL1 denoted MYCL2 (DePinho et al. 1987; Morton et al. 1989; Arnason et al. 1998) that is intronless and presumably arose through a reverse transcription event. Similarly, the murine lineage has an additional MYC family member, S-MYC, presumably formed by a MYCN cDNA sequence reintegrating into the genome (Sugiyama et al. 1989, 1999; Doskocil 1996). Another MYC homolog, B-MYC, exists in the mammalian lineage and lacks the carboxy-terminal bHLHZ sequence (Ingvarsson et al. 1988; Asker et al. 1995). Although B-MYC cannot dimerize with MAX or bind DNA, it appears to associate with other MYC amino-terminal-binding proteins (Burton et al. 2006). Targeted deletion of B-MYC in mice leads to increased MYC levels accompanied by apoptosis and decreased spermatogenesis (Turunen et al. 2012).

Based on the homologous bHLHZ domain that defines the interaction among network members, each of the MAX, MLX, MYC, MNT, MXD, Mondo, and MGA orthologous protein groups distinctly cluster, with paralogs forming distinguishable subgroups and orthologous sequences generally reflecting species divergence (Fig. 6). Nematodes are the exception, with more divergent but clearly related bHLHZ sequences. This indicates that the protein and DNA interactions of network members are largely conserved in animals. Moreover, other functional domains including the MYC boxes (MBI-IV) and Mondo conserved regions (see O'Shea and Ayer 2013) have been preserved throughout animal evolution (McFerrin and Atchley 2012). The level of sequence and functional conservation of network members, even in the most primitive animals, implies that the MAX and MLX networks are involved in fundamental cellular functions dating back millions of years to the emergence of animals.

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