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Targeting MYC Proteins for Tumor Therapy

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Abstract

Targeting the function of MYC oncoproteins holds the promise of achieving conceptually new and effective anticancer therapies that can be applied to a broad range of tumors. The nature of the target however—a broadly, possibly universally acting transcription factor that has no enzymatic activity and is largely unstructured unless complexed with partner proteins—has so far defied the development of clinically applicable MYC-directed therapies. At the same time, lingering questions about exactly which functions of MYC proteins account for their pervasive oncogenic role in human tumors and need to be targeted have prevented the development of effective therapies using surrogate targets that act in critical MYC-dependent pathways. In this review, we therefore argue that rigorous testing of critical oncogenic functions and protein/protein interactions and new chemical approaches to target them are necessary to successfully eradicate MYC-driven tumors.

1. MYC PROTEINS AS TARGETS FOR TUMOR THERAPY: THE PROMISE

The *MYC* family of proto-oncogenes has three members: *MYC*, *MYCN*, and *MYCL*. An overwhelming body of evidence argues that targeting the function or expression of these proteins is a valid and rewarding aim for tumor therapy. This notion is based on three major lines of evidence.

First, expression of MYC proteins is enhanced and deregulated in many human tumors. Although the precise percentage is unknown, the consensus is that most individual human tumors show deregulated expression of either *MYC*, *MYCN*, or *MYCL*. The major difference between the three *MYC* isoforms is the type of tumor in which they are derepressed: While deregulation of *MYC* is pervasive, enhanced expression of *MYCN* is restricted to a limited number of neuronal or neuroendocrine entities (Rickman et al. 2018), and deregulated expression of *MYCL* is predominantly found in small-cell lung carcinoma (Bragelmann et al. 2017). In addition, there are entities in which the *MYC* paralogs enforce different transformed phenotypes, demonstrating that there are functionally relevant differences (Kawauchi et al. 2012, Vo et al. 2016). There is a plethora of causes for enhanced *MYC* expression in individual tumors, which include alterations in the *MYC* genes themselves, such as translocations that fuse strong enhancers to the *MYC* coding sequence, or amplifications of *MYC* family genes. Sequencing human tumor genomes has also uncovered a sizeable number of point mutations, which include some hotspot mutations. However, most tumors show enhanced expression of wild-type MYC proteins. Importantly, mutations in multiple upstream regulators, involved in the control of each step of MYC protein biogenesis and turnover, are frequent oncogenic events, and the common denominator of these changes is to enhance MYC protein expression. MYC proteins are part of a network of interacting helix-loop-helix (HLH) proteins, and some of the complexes of this network, e.g., the MNT/MAX complexes, antagonize MYC transcriptional function. A recent systematic genomic analysis has demonstrated that altered expression and mutations in other members of this network expand the range of tumors in which MYC function is perturbed (Schaub et al. 2018).

Second, there is an overwhelming body of evidence demonstrating that deregulated expression of *MYC* causally contributes to tumorigenesis and is required to maintain tumor growth. This argument rests on multiple observations documenting that (*a*) deregulated expression of *MYC* in tissue culture elicits many hallmarks of oncogenic transformation, such as deregulated growth and proliferation; (*b*) overexpression of *Myc* induces tumorigenesis in a wide range of transgenic models (Gabay et al. 2014); (*c*) tumors that are established by either doxycycline-regulatable or MYCER-conditional proteins continue to depend on MYC function even after establishment (Felsher & Bishop 1999); and (*d*) depletion of not-mutated endogenous Myc abolishes tumorigenesis in models of colon carcinogenesis driven by the loss of the *Apc* gene (Sansom et al. 2007) and of pancreatic carcinomas driven by mutant *Kras* and deleted *TP53* (Vaseva et al. 2018).

Third, targeting MYC opens a potentially wide therapeutic window for tumor therapy. Either alone or in combination with their paralogs, *Myc* genes are essential for normal development (Dubois et al. 2008, Trumpp et al. 2001) as well as for homeostasis of individual tissues, including intestine (Muncan et al. 2006), skin (Zanet et al. 2005), and the hematopoietic compartment (Wilson et al. 2004). Nevertheless, partial depletion or inhibition of Myc is compatible with normal tissue function but delays tumorigenesis in animal models. For example, mice with only one *Myc* allele have no phenotype during normal development, but show strongly impaired and delayed tumorigenesis. Specifically, expression of a dominant-negative allele of *Myc* termed *Omomyc* (Jung et al. 2017, Soucek et al. 2004) leads to tumor regression and long-term survival in mouse models of lung (Soucek et al. 2008, 2013), glioma (Annibali et al. 2014), and pancreatic islet tumors (Sodir et al. 2011), although none of these tumor models is driven by a *Myc* transgene.

It has been difficult to pinpoint specifically which aspect of tumor physiology establishes the dependence of tumor cells on elevated MYC levels, raising the question, What may be the critical therapeutic endpoint of a MYC-directed therapy? Inhibition of *MYC* in culture inhibits proliferation and cell growth but usually does not cause apoptosis or provoke an irreversible cell cycle arrest, termed senescence. In contrast, transient inhibition or deletion of *MYC* in tumors in vivo induces tumor regression. In some models, the difference is due to Myc- or MycN-dependent trophic signals from tumor cells that are required to maintain the tumor vasculature (Chanthery et al. 2012, Sodir et al. 2011), arguing that a collapse of the tumor vasculature is a relevant endpoint of a MYC-directed tumor therapy. In addition, the regression that occurs upon MYC inhibition or deinduction in lymphomas and carcinomas of the lung requires lymphocyte and natural killer cell function. It is likely, therefore, that restoration of immune surveillance and induction of immune cell–mediated killing are a second critical endpoint of targeting MYC in vivo (Casey et al. 2016, Kortlever et al. 2017, Topper et al. 2017).

2. THE STRUCTURE AND FUNCTION OF MYC: THE CHALLENGE

MYC proteins are nuclear proteins that bind to DNA as heterodimers with a partner protein termed MAX (Dang 2012, Kress et al. 2015). MYC and MAX interact with each other via an HLH leucine zipper domain located at the C terminus of the MYC protein (**Figure 1*a***). In vitro, the heterodimer binds to a specific DNA sequence termed E-box with a core CACGTG sequence. In contrast to most other HLH proteins, sequence discrimination by MYC/MAX heterodimer is not very strict, and the sites to which MYC binds in vivo are determined by multiple protein/protein interactions in addition to the DNA target sequence (Guo et al. 2014, Lorenzin et al. 2016). For example, interactions with WDR5 and PAF1 contribute to MYC's affinity to chromatin (Gerlach et al. 2017, Thomas et al. 2015). While levels of MYC proteins in normal cells are low, they can reach up to a million molecules per cell in tumor cells; as a consequence, binding sites can be saturated and binding patterns appear to determine the differences in affinity of MYC for each site (Lorenzin et al. 2016).

In the absence of MAX, the C terminus of MYC has very little structure. Similarly, the entire amino terminus of MYC is considered to be intrinsically unstructured when not in complex with other proteins. The crystal structure of fragments of MYC or MYCN that are bound to WDR5 and Aurora-A also show that amino-terminal domains of MYC, like the DNA-binding domain, can stably fold when bound to protein partners (**Figure 1*a***) (Richards et al. 2016, Thomas et al. 2015). Both the C terminus and the complex with Aurora-A have been successfully disrupted by small molecules, and these molecules have therapeutic efficacy (see below), suggesting that resolving the structure of other critical MYC complexes and using this knowledge to disrupt these complexes are promising ways to target MYC.

Currently, three biochemical functions of MYC are documented that may account for its oncogenic function. First, MYC increases the relative expression of many functionally diverse downstream target genes, and this may cause transformation (Pelizzola et al. 2015). While it has been notoriously difficult to pinpoint a core of MYC target genes that are conserved across different biological systems or tumor entities, most observations are compatible with broad positive effects of MYC on genes involved in protein translation and nucleotide biosynthesis (**Figure 1*b***) (Muhar et al. 2018). A conceptually related model proposes that global positive effects of MYC on the function of RNA polymerase II (RNAPII) at all active promoters are critical for transformation (Lin et al. 2012, Nie et al. 2012). This model has been termed the amplifier model of MYC function. It is based on observations that MYC proteins globally affect the function of RNAPII at core promoters and can enhance recruitment of RNAPII to promoters (de Pretis et al.

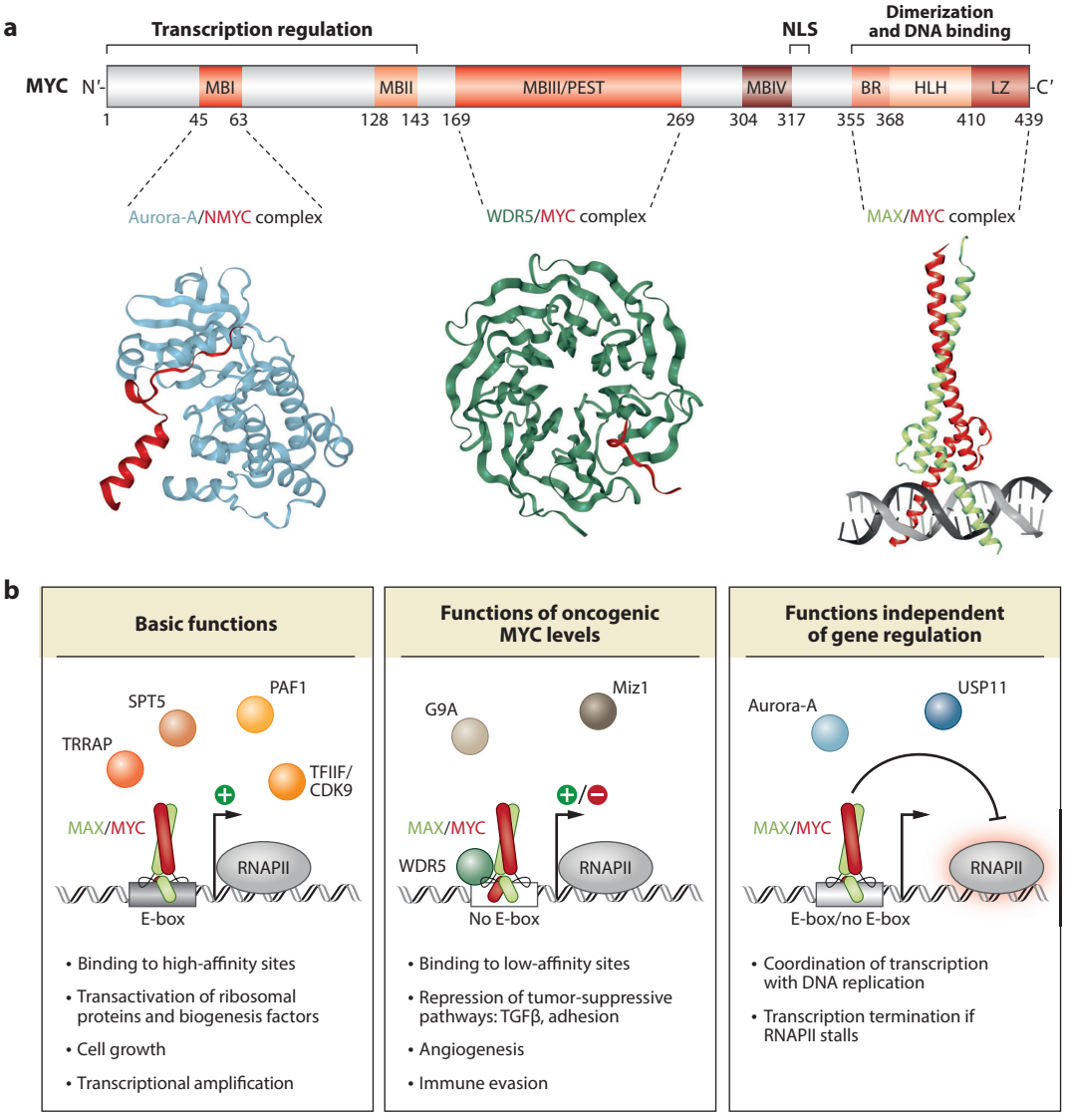

Figure 1

(*a*) The structure of MYC. MBI–MBIV are the so-called MYC boxes, a term coined to describe short, evolutionary conserved amino acid sequences among MYC proteins. Shown are three complexes of MYC proteins that have been resolved and their structures. Amino acid numbers are from human MYC. (*b*) Possible critical oncogenic functions of MYC. Physiological levels of MYC are required for cell growth and cell proliferation, and it is possible that maintaining the expression of the responsible genes is the critical oncogenic function of MYC. However, many tumors express clearly supraphysiological levels, and such levels of MYC regulate different genes, such as those involved in angiogenesis and immune evasion. Finally, MYC proteins have transcriptional functions that are not immediately relevant for gene expression, such as the coordination of transcription with DNA replication. Abbreviations: BR, basic region; HLH, helix-loop-helix; LZ, leucine zipper; NLS, nuclear localization sequence; PEST, proline-, glutamic acid-, serine-, and threonine-rich sequence.

2017), enhance promoter escape (Buchel et al. 2017), release RNAPII from the pause site (Rahl et al. 2010, Walz et al. 2014), suppress early termination (Chiu et al. 2018, Herold et al. 2019), and enhance RNAPII processivity during elongation (Baluapuri et al. 2019). Collectively, the model suggests that increasing the expression of many anabolic or even all expressed genes may be critical for MYC-dependent transformation. As a consequence, strategies that, for example, globally inhibit transcription have been explored for targeting MYC-dependent tumors (see below).

While most active promoters bind MYC, as described above, it has recently been recognized that active genes differ widely in their affinity for MYC; hence, physiological and oncogenic levels of MYC regulate different sets of target genes (Lin et al. 2012, Lorenzin et al. 2016). While high-affinity genes are involved in biosynthetic functions as described above, the functions and the responses to MYC of low-affinity genes are more diverse. For example, the ability of MYC to repress genes involved in TGFβ signaling (van Riggelen et al. 2010) and immune recognition of tumor cells (Kortlever et al. 2017, Topper et al. 2017) contributes to MYC-dependent tumor growth. It is possible, therefore, that the transforming functions of MYC proteins are specifically related to their ability to regulate low-affinity genes. Mechanistically, this concept can explain the existence of a therapeutic window, since low-affinity target genes are regulated selectively by high MYC levels. If tumors are addicted to the expression of these genes, they will be addicted to high MYC levels (Lorenzin et al. 2016). Notably, OmoMYC displaces endogenous MYC only from a subset of target sites and blunts target site invasion by high-MYC levels (Jung et al. 2017). It is possible, therefore, that this explains the tumor-selective effects of OmoMYC expression.

Recently, large-scale proteomic and BioID analyses have revealed an astonishing complexity of the MYC and MYCN interactomes, since both MYC and MYCN interact with large sets of functionally diverse partner proteins (Baluapuri et al. 2019, Buchel et al. 2017, Kalkat et al. 2018). Functional annotation of the interacting proteins suggests that the transcriptional functions of MYC proteins are much broader than previously anticipated. While the function of some of the complexes can be linked to specific effects of MYC on chromatin structure and basal transcription (Baluapuri et al. 2019, Jaenicke et al. 2016), other complexes point to transcriptional functions of MYC that are not linked to changes in expression of downstream target genes. For example, complexes of MYCN with USP11 recruit BRCA1 to terminate transcription when RNAPII is stalling at core promoters, thereby effectively clearing promoters where RNAPII is blocked by, for example, excessive torsional stress (Herold et al. 2019). This ability of MYCN may enable cells to cope with stress situations that impinge on transcription, e.g., nucleotide deprivation or oxidation of nucleotide pools. Complexes of MYCN with Aurora-A form during S phase and coordinate transcriptional elongation with DNA replication (Buchel et al. 2017). Finally, complexes of MYC with unknown partner proteins position genes within the cell nucleus, a process that is also linked to escape from replication stress (Su et al. 2018, Teloni et al. 2019). Collectively, these observations suggest that the ability to reshape promoters in response to stress situations or during the cell cycle may be a critical oncogenic function of MYC. Like the general amplifier model, it suggests that global rather than gene-specific functions of MYC are critical for MYC-dependent transformation, but that oncogenic functions could be independent of changes in mRNA (messenger RNA) levels of target genes.

At this point, it has not been rigorously established which of these models (**Figure 1*b***) best accounts for the pervasive transforming capacity of deregulated MYC expression in human tumors.

3. TARGETING MYC DIRECTLY

Several attempts to target MYC directly are in the experimental stage (**Figure 2**). Numerous compounds have been identified that inhibit the ability of MYC to heterodimerize with MAX, the

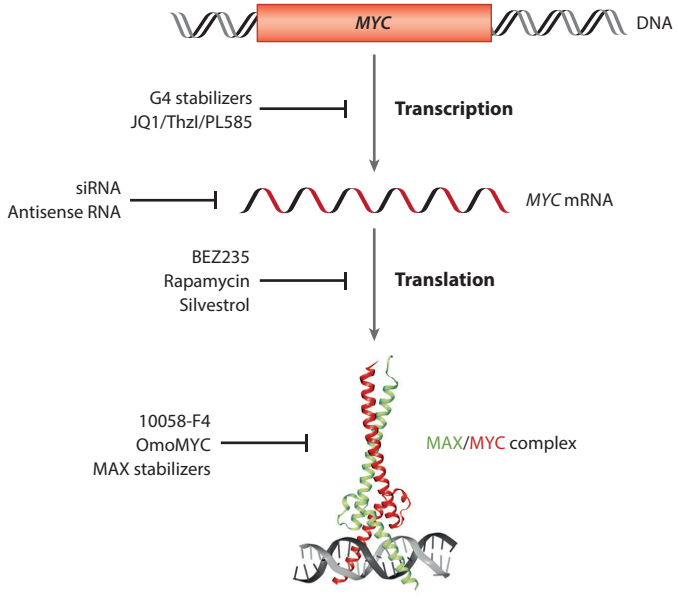

Figure 2

Summary of strategies targeting MYC expression and function. These strategies attempt to reduce the expression and impair the function of MYC at multiple levels. Synthetic lethal strategies are not shown, and strategies that exploit the ubiquitination system to degrade MYC are discussed in **Figure 3**. Abbreviations: mRNA, messenger RNA; siRNA, small interfering RNA.

best characterized of which is 10058-F4 (Yin et al. 2003). In tissue culture, addition of 10058-F4 at concentrations of 10–100 μM displaces MYC and MYCN from chromatin and reverts MYC-dependent effects on RNAPII, as well as changes in gene expression (Nie et al. 2012). Treatment of mice with 10058-F4 delays tumor growth and prolongs survival in a transgenic model of neuroblastoma (Zirath et al. 2013). A related concept is based on the idea of displacing MYC from MYC/MAX heterodimers by stabilizing MAX homodimers (Jiang et al. 2009). A new generation of such compounds has just been described (Struntz et al. 2019) that reduce MYC chromatin occupancy, antagonize MYC-dependent gene expression in cells at concentrations around 10 μM, and delay growth of MYC-driven tumors in vivo. Another strategy is to deliver OmoMYC directly as a therapeutic peptide (Beaulieu et al. 2019). When added to cells in culture, the OmoMYC peptide translocates into nuclei, displaces endogenous MYC from its cognate binding sites, and antagonizes MYC-dependent gene expression. Upon injection in vivo, OmoMYC retards tumor growth, suggesting that it can also antagonize MYC's oncogenic function in vivo.

Another two concepts are currently being explored that may significantly accelerate and alter strategies to target MYC directly. The first is the notion that small-molecule ligands can generate or strengthen a molecular link between a target protein and one of several ubiquitin ligases (Sakamoto et al. 2001). While these molecules, termed PROTACs (proteolysis-targeting chimeras) or degronomids, are bifunctional in nature since they link a target protein to the cereblon or VHL ubiquitin ligase, it is conceivable that chemical screens can identify simpler scaffolds that enhance the affinity of one of the natural ubiquitin ligases of MYC. The second concept is that transcriptional activation takes place in phase-separated domains in which enhancers and the transcription machinery come together (Boija et al. 2018). If MYC proteins contribute to phase separation and

if this is relevant for their oncogenic function, compounds may be identified that disrupt MYC-dependent transcription hubs rather than target specific protein/protein interactions of MYC.

4. TARGETING *MYC* EXPRESSION

As direct inhibition of MYC proteins is challenging, many efforts instead focus on the identification of compounds that decrease *MYC* expression. Over the last decades, various strategies have been developed to decrease *MYC* transcription, destabilize *MYC* mRNA, or attenuate its translation (**Figure 2**).

Thirty years ago, attempts were made to silence *MYC* mRNA by antisense oligonucleotides (Clarke et al. 1988) or RNAs mediating RNA interference (Li et al. 2013, Sklar et al. 1991). Although results were initially promising, leading to various studies including phase I trials (Devi et al. 2005), all clinical attempts were discontinued due to poor drug stability and delivery problems. Efforts to improve the delivery and use of oligonucleotide-based therapeutics are ongoing.

Alternative approaches intend to reduce transcription of *MYC* (**Figure 2**). Early work identified G-quadruplex (G4) structures as repressive elements in the MYC promoter (Simonsson et al. 1998). Small molecules stabilizing the G4 conformation induce promoter silencing and *MYC*-level reduction (Rangan et al. 2001, Siddiqui-Jain et al. 2002). One of several developed compounds, CX-3543, reached clinical phase II studies but appeared to act, at least partially, via *MYC*-independent mechanisms (Drygin et al. 2009, Xu et al. 2017). This exemplifies the challenge to obtain drugs that exclusively decrease the transcription of *MYC*, and it is unclear if target specificity can be at all achieved.

Surprisingly, even transcriptional inhibitors with low target-gene specificity appear to exhibit antitumor activity via inhibiting MYC function. One example is the thieno-triazolo-1,4-diazepine JQ1, which was developed as an inhibitor of the bromodomain and extraterminal (BET) subfamily of human bromodomain proteins (BRD2, BRD3, and BRD4) (Filippakopoulos et al. 2010). BET proteins activate transcription by binding to acetylated lysine residues of histones and recruiting RNAPII coactivators like P-TEFb (Bisgrove et al. 2007). Initially intended to inhibit the activity of P-TEFb at *MYC* target genes, it was unexpectedly observed that expression of *MYC* itself was affected most upon treatment of multiple myeloma cells with the BET inhibitor JQ1 (Delmore et al. 2011). Although BET proteins like BRD4 are believed to act as global activators of transcription (Muhar et al. 2018), the selectivity of JQ1 and other BET inhibitors toward *MYC* transcription could result from BET protein clusters on large enhancer regions (called super-enhancers) in proximity of *MYC* (Loven et al. 2013), but it could also result from *MYC*'s extraordinarily short mRNA and protein half-life. Dozens of distinct BET inhibitors are currently being tested in clinical trials for their safety and effectiveness against various hematopoietic and solid tumor entities, including multiple myeloma, glioblastoma, and prostate cancer (Stathis & Bertoni 2018). While many phase I and II studies are ongoing, some were terminated due to intolerable toxicity (Postel-Vinay et al. 2019), which may result from transcriptional inhibition of genes other than *MYC*. Based on the PROTAC concept, BET inhibitors were also used to develop small molecules that induce degradation of BET proteins (Raina et al. 2016, Winter et al. 2017). These remain to be investigated for their potency as anticancer drugs.

Similar to BET inhibitors, inhibition of transcription-associated cyclin-dependent kinases (CDKs) is being tested as an antitumor therapy (Chipumuro et al. 2014, Christensen et al. 2014, Kwiatkowski et al. 2014, Walsby et al. 2011). Indeed, the mode of action of CDK inhibitors has been attributed to their ability to decrease the expression of *MYC* or *MYCN*. Finally, small molecules targeting eukaryotic translation initiation factors were identified as potent inhibitors of

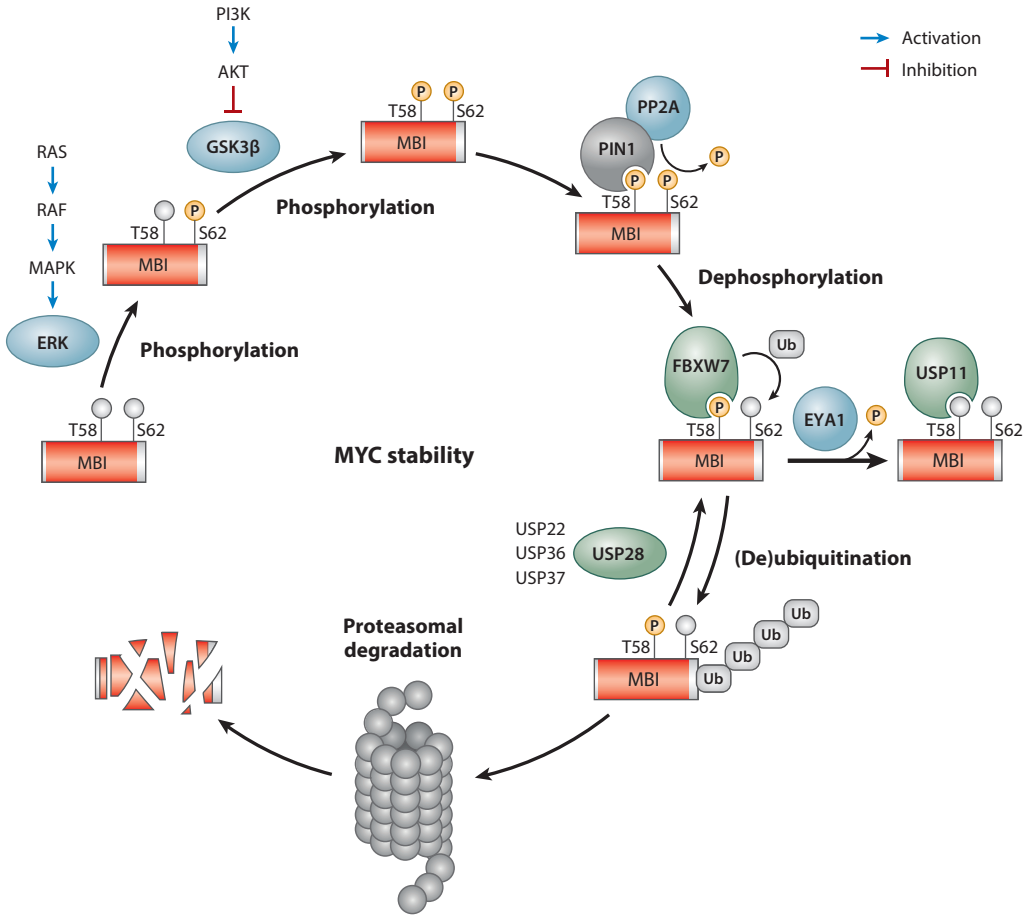

Figure 3

MYC ubiquitination by FBXW7 and its regulation. While up to 20 different ubiquitin ligases have been documented to affect MYC stability and function, this is currently the best-understood pathway. The critical residue recognized by FBXW7 is phosphorylated T58. Phosphorylation of this residue is carried out by GSK3 after a priming phosphorylation at S62, which can be carried out by multiple cyclin-dependent and MAP kinases. T58 can be dephosphorylated and is then recognized by a deubiquitinating enzyme, USP11. Other deubiquitinating enzymes that enhance MYC stability include USP28, USP36, and USP37, but they appear to recognize MYC via a primary interaction with FBXW7. Abbreviations: MBI, MYC box I; S62, serine 62; T58, threonine 58.

both cap- and IRES (internal ribosome entry site)-dependent translation of *MYC* with therapeutic potential (Schatz et al. 2011, Wiegering et al. 2015).

5. TARGETING MYC STABILITY

All MYC proteins are highly unstable proteins that are continuously turned over by the ubiquitin/proteasome system. At this point, approximately 30 individual ubiquitin ligases have been described that associate with either MYC or MYCN and affect their stability and their function. The best-understood pathway centers on a degron that is located in a highly conserved stretch of amino acids termed MBI (MYC box I; see **Figure 3**). The critical residue is threonine 58 (T58): When phosphorylated, this residue is recognized by the FBXW7 (Welcker et al. 2004) and FBXL3

ubiquitin ligases (Huber et al. 2016); dephosphorylated T58 is recognized—possibly indirectly—by the USP11 deubiquitinating enzyme (Herold et al. 2019). In addition to USP11, the USP28 (Diefenbacher et al. 2014, 2015; Popov et al. 2007; Schulein-Volk et al. 2014), USP7, USP22, USP36, and USP37 deubiquitinating enzymes can also stabilize MYC or MYCN proteins. Very recently, specific inhibition of individual deubiquitinating enzymes has been achieved (Turnbull et al. 2017). It is therefore likely that the ability of USP inhibitors to reduce cellular MYC levels and control MYC function will soon be explored.

T58 is phosphorylated by glycogen synthase kinase 3 (GSK3β) downstream of a complex signaling cascade (Farrell & Sears 2014). This cascade is initiated by several MAP- and cyclin-dependent kinases inducing phosphorylation at serine 62 (S62) of MYC, which itself activates transformation. This phosphorylation can prime GSK3 to phosphorylate T58, but the subsequent recognition by FBXW7 requires dephosphorylation of S62 by protein phosphatase PP2A. As consequence, inhibition of PP2A-mediated MYC S62 dephosphorylation by endogenous PP2A inhibitors like CIP2A is a critical transforming event, and several tumor cells have been shown to depend on PP2A inhibitors (Westermarck & Hahn 2008). Indeed, several ways have been explored to promote MYC turnover, including the blockade of PI3K (to enhance GSK3 function) or small-molecule activators of PP2A (Janghorban et al. 2014). However, such interferences are likely to be very pleiotropic, and it is currently unclear whether the observed therapeutic effects, e.g., in response to PI3K inhibition, are due to increases in MYC turnover.

In several tumors, access of FBXW7 to the degron is blocked by a direct complex of MYCN and MYC with the Aurora-A kinase (Dauch et al. 2016, Otto et al. 2009, Richards et al. 2016). This generates a unique chance to target MYC stability, since certain Aurora-A ligands disrupt the complex and cause degradation of MYC and MYCN in several mouse tumor models (Brockmann et al. 2013, Dardenne et al. 2016, Hill et al. 2015). One of these inhibitors, alisertib, has strong therapeutic effects in preclinical models and has been explored for the therapy of human MYCN–driven tumors (Dubois et al. 2018). The clinical results reveal a dose-limiting toxicity, which precludes a clear evaluation of therapeutic efficacy. More recently, we have shown that a critical function of the Aurora-A complex with MYCN is to inhibit MYCN-driven transcriptional elongation during S phase in order to coordinate MYCN-driven transcription with DNA replication (Buchel et al. 2017). This finding argues that combining Aurora-A inhibitors with drugs that attenuate the ability of cells to deal with replication stress is a feasible way to escape the toxicity of a monotherapy using high levels of Aurora-A inhibitors.

6. TARGETING COFACTORS OF MYC

The growing knowledge about cofactors of MYC has sparked several attempts to target cofactors with enzymatic activity for therapy of MYC-driven tumors. A central example is a strategy to target WDR5 to destabilize MYC binding to its target sites (Aho et al. 2019). A second strategy is based on the finding that ubiquitin-mediated degradation of MYC not only limits MYC levels but also has a positive role in MYC transactivation (Adhikary et al. 2005, Kim et al. 2003, von der Lehr et al. 2003). Ubiquitinated MYC is bound by and subsequently extracted from chromatin by VCP ATPase (Heidelberger et al. 2018). This process facilitates the transfer of MYC-bound elongation factors onto RNAPII (Jaenicke et al. 2016). As a consequence, small-molecule inhibitors of the HUWE1 ubiquitin ligase abrogate MYC-dependent transcriptional regulation in colon tumor cells, and the same is true for small-molecule inhibitors of the VCP protein (Heidelberger et al. 2018, Peter et al. 2014). The therapeutic development of these strategies will require HUWE1 inhibitors that can be explored in vivo. The comprehensive identification of MYC-interacting proteins in various cellular entities (Baluapuri et al. 2019, Buchel et al. 2017)

allows for the systematic identification of—potentially druggable—protein/protein interactions, which are essential for MYC's oncogenic capacity.

7. TARGETING SPECIFIC DEPENDENCIES OF MYC-DRIVEN TUMOR CELLS

High-level expression of MYC proteins is stressful for cells, and tumors expressing deregulated levels of MYC depend on several specific factors for survival, including an enhanced dependence on antiapoptotic proteins and trophic signals (Pelengaris et al. 2002), glutamine as nutrient source (Dejure et al. 2017, Gao et al. 2009), splicing factors (Hsu et al. 2015), and AMP-dependent kinases, which are activated by an increase in cellular AMP levels (Kfoury et al. 2018, Liu et al. 2012). Several of these dependencies can be addressed with available or recently developed small-molecule inhibitors. For example, the enhanced energy demand of MYC-driven tumors can be targeted with antibiotics that inhibit mitochondrial translation (D'Andrea et al. 2016), and the dependence of glutamine supply can be targeted with small-molecule inhibitors of glutaminase, which is the enzyme that converts glutamine to glutamate. As consequence, a glutaminase inhibitor has been explored in multiple clinical trials, some of which used amplifications of MYC to stratify patients. A recent study demonstrated that the rampant apoptosis resulting from targeting the dependence of breast cancer cells expressing high levels of MYC on AMPK dramatically enhances therapy with checkpoint-blocking inhibitors (Haikala et al. 2019), thereby revealing a surprising cross-talk of the cellular energy metabolism with immune surveillance.

8. CONCLUDING REMARKS

In our view, four conclusions can be drawn about current approaches to target MYC. First, all available genetic and chemical evidence suggests that direct targeting of complexes of MYC and MYCN is likely to be successful; however, for the currently best-validated complex, MYC and MAX, we are lacking a chemical breakthrough that will bring compounds disrupting this complex into the clinic.

Second, blocking upstream regulators, e.g., blocking MYC expression, or enhancing MYC turnover is chemically feasible and can be therapeutically effective; however, all factors that regulate MYC also target many other genes or proteins. Hence, it is an open question whether any therapeutic effect of such strategies depends specifically on their ability to target MYC.

Third, interfering with effector functions of MYC is also often chemically feasible. These strategies are mainly limited by an incomplete understanding of critical oncogenic effector functions of MYC. Therefore, targeting biochemical processes that MYC has been implicated in, such as basic transcription, protein translation, or nucleotide biosynthesis, or disrupting the coordination of transcription with DNA replication is currently not unequivocally linked to targeting MYC.

Finally, a promising strategy forward is to use new and still-emerging proteomic information to determine the biological relevance and three-dimensional structure of MYC protein complexes and to identify new inhibitors and PROTACs targeting these complexes.

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