Review Article

Mammalian MYC Proteins and Cancer

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The MYC family of proteins is a group of basic-helix-loop-helix-leucine zipper transcription factors that feature prominently in cancer. Overexpression of MYC is observed in the vast majority of human malignancies and promotes an extraordinary set of changes that impact cell proliferation, growth, metabolism, DNA replication, cell cycle progression, cell adhesion, differentiation, and metastasis. The purpose of this review is to introduce the reader to the mammalian family of MYC proteins, highlight important functional properties that endow them with their potent oncogenic potential, describe their mechanisms of action and of deregulation in cancer cells, and discuss efforts to target the unique properties of MYC, and of MYC-driven tumors, to treat cancer.

1. Introduction

MYC is an oncoprotein transcription factor that features in the cancer-related deaths of an estimated 100,000 people in the United States—as well as millions worldwide—every year. Its formidable oncogenic reputation stems from its frequent deregulation in a host of human cancers and from a suite of activities that place MYC at the nexus of cell growth, proliferation, metabolism, and genome stability. The purpose of this review is to introduce readers to the basic features of mammalian MYC proteins and distill key concepts and general themes in what is known about the molecular processes through which MYC drives tumorigenesis. Along the way, we will also discuss controversial or unresolved issues that limit current understanding of MYC proteins and highlight areas that are ripe for exploration in the future. My intention is to leave the reader with the sense that MYC possesses a unique and expansive set of activities that underlie its place as a major human oncoprotein and may well hold the key to development of broadly effective anticancer therapies.

2. MYC: The Early Years

MYC is arguably one of the most well-studied proteins in human history. More than 22,000 primary and review articles have been written on this topic, which in recent years have been appearing at an average rate of almost three publications

per day (Figure 1). MYC has been studied by virologists, geneticists, molecular biologists, structural biologists, cell biologists, biochemists, and theoretical biologists, and countless millions of dollars have been spent interrogating both its normal and its cancer-relevant functions. In any subject as expansive and as lasting as this, it is impossible to provide a comprehensive review of all of the major discoveries that have shaped current thinking on the MYC proteins. But as the origins of this field are fading quickly into history, it is worthwhile to reflect briefly on the early studies that germinated the MYC phenomenon.

The discovery of MYC stemmed directly from experiments begun in the early 1960s, but the crucial context for those experiments was established a half a century before by Peyton Rous, who showed that cell-free filtrates from a chicken sarcoma could be used to transmit disease to susceptible animals [2]. This ground-breaking work ultimately led to the discovery of retroviruses and viral oncogenes (and their cellular counterparts) [3], but crucially it spurred researchers to exploit avian leukosis viruses as a way to unlock the basis of cancer. Framed in this setting was the isolation in 1964 of MC29, a strain of virus propagated from a Rhode Island Red chicken in Sofia, the capital city of Bulgaria [4]. The hen had succumbed to a spontaneously developed hematological disease that included anemia and solid tumors of promyelocytic character. Subsequent isolation and passaging of the virus in animals revealed that MC29 induces

FIGURE 1: Timeline of studying MYC. The figure shows the annual number of publications on MYC proteins from 1964 to 2012, as listed on the NCBI's PubMed website, along with approximate timing of key discoveries in the MYC field during that time. Citations from the period 1964–1980 were recovered using the search term “MC29.” The search excludes instances where MYC refers to use of the MYC epitope tag. See text for more detailed description of key discoveries.

neoplasia predominantly in the hematopoietic compartment of recipient fowl [4, 5] but differs from other avian leukosis viruses in that it does not typically result in development of leukemia. Instead, MC29 transforms myeloid cells to form either diffuse growths—myelocytomatosis—or solid tumors—myelocytomas. It was this unique disease spectrum that ultimately gave MYC its name (*myelocytomatosis*).

Following the initial characterization of the virus, the hunt began for identification of the genetic basis of its tumorigenicity. This was not a trivial feat, as early researchers did not have access to rapid assays of tumorigenesis or advanced molecular biology tools nor did they formally know that MC29 carried a *bona fide* oncogene—its oncogenic properties, for example, could have resulted from its influence on the expression of a cellular oncogene. Ultimately, dissection of the oncogenic activity of MC29 was facilitated by a number of crucial technological developments and by inherent characteristics of the virus itself. The demonstration that MC29 could act in a variety of isolated cell types to induce transformation [6–10]—the acquisition of phenotypic changes that resemble those displayed by tumor cells *in vivo*—provided researchers with a rapid and reliable proxy for assaying its tumorigenic function. The virus itself was fairly easy to grow to high titer in tissue culture, and as we now know carries just a single functional gene, the *gag-myc* fusion [11–13]. Importantly, development of molecular biology approaches, especially the ability to radiolabel specific nucleic acid sequences and to interrogate genome structure by solution hybridization, gave researchers the tools they needed to molecularly characterize the virus. Indeed, in just a short period of time in the late 1970s the candidate *v-myc* gene was identified [13, 14], shown to be distinct from the *src* oncogene present in Rous's original virus [15], and found to have a cellular homolog in uninfected vertebrate cells [16, 17], consistent with Bishop and Varmus's model for the cellular origin of retroviral oncogenes [18]. The presence of *v-myc* sequences

in related oncogenic retroviruses [19], together with findings that expression of a cellular *v-myc* homolog is greatly stimulated by retroviral promoter insertion of a distinct avian leukosis virus [20–22], cemented the idea that MYC is the bona fide oncogene within MC29. Finally, in 1982, the *c-myc* gene was cloned and characterized [23], an event that ushered in a new era of exploration of the molecular mechanisms of tumorigenesis and triggered a massive wave of research into MYC's regulation, structure, and functions (Figure 1).

As indicated in Figure 1, the MYC boom of the 1980s resulted in fundamental new insight into MYC, and these studies in turn led to development of key concepts in tumorigenesis, such as oncogene cooperation [24] and the importance of apoptosis [25–27] as a tumor surveillance mechanism. Many of these discoveries form the basis of material discussed throughout this review. Looking at the pace of MYC research over recent years, it is interesting to note that we are currently in the midst of a second “MYC rush” that began around 2006, undoubtedly triggered by the advent of genomic approaches towards studying MYC and fueled by discoveries that MYC is one of the “magic four” [28, 29] factors that can reprogram differentiated cells to the induced pluripotent stem cell (iPS) state. Given the intense interest in MYC and the ever-expanding universe of MYC functions, it seems certain that the current rush will continue if not accelerate for years to come.

3. The MYC Family of Proteins

The *c-myc* gene first identified in 1982 is the prototype for a family of related proteins (Figure 2) that are not only conserved across metazoan life [30] but can be found in similar form and function in premetazoan organisms such as choanoflagellates [31]. In mammalian cells, MYC proteins arise from three distinct gene family members—*c-Myc*, *N-myc*, and *L-myc*—which function in a similar manner

FIGURE 2: Architecture of the MYC family. The image at the top shows a generic representation of a mammalian MYC protein, indicating the transcriptional activation domain, the central portion, the canonical nuclear localization sequence (N), and the region involved in DNA binding via interaction with MAX. Below is a representation of conserved sequences present in C-, N-, and L-MYC family members. c-MYC is drawn to scale at 439 amino acids. N- and L-MYC proteins are different lengths (464 and 364 amino acids, resp.) due to differences in the length of nonconserved sequences but are drawn to highlight the conservation and relative location of MYC boxes.

but display notable differences in potency [32, 33] and patterns of expression [34–36]. Rodents also express a *B-myc* variant that shares homology with the amino-termini of MYC proteins [37] but this has yet to be characterized in other mammals. The presence of multiple MYC family members with distinct expression patterns undoubtedly reflects different spatial and temporal requirements for MYC activity, both in development and in the adult animal [38], and is most frankly seen in the particular way each gene is overexpressed in specific cancer types [34, 39, 40]. *c-Myc* is broadly overexpressed in both blood-borne and solid tumors. *N-myc* is most frequently overexpressed in solid cancers of neural origin, such as neuroblastoma and glioma. And *L-myc* is most often overexpressed in small cell lung carcinomas. Given the conservation of these proteins, it is reasonable to assume that the mechanisms through which they drive tumorigenesis are similar, although it is also important to recall that most functional studies of MYC to date have focused on the archetypal *c-Myc* product.

As well as multiple family members, a number of *c-Myc* protein variants can be generated by mechanisms that include alternative start codon usage (referred to as “p67” and “p64” [41, 42]), downstream translation initiation within the MYC mRNA (“Myc-S;” [43]), and site-specific proteolysis (“MYC-nick;” [44]). Although these variants are intriguing, they have received comparatively little attention and hence their significance to cancer, for the most part, is not well understood.

3.1. The Anatomy of MYC. The general architecture of mammalian MYC proteins resembles those of a typical sequence-specific DNA-binding transcriptional regulator (Figure 2). At the amino-terminus of MYC lies its transcriptional activation domain (TAD), a region that is sufficient for transcriptional activation when fused to a heterologous DNA binding domain (DBD) [45] and is required for MYC’s transforming activity *in vitro* [46]. This region is accepted to be the primary element within MYC that contacts RNA polymerase II-associated proteins to stimulate gene induction. Like many TADs, the MYC TAD is intrinsically unstructured in the

absence of partner proteins [47], is enriched in acidic, proline, and glutamine residues, and retains its ability to stimulate transcription in organisms that do not have MYC proteins, such as the yeast *Saccharomyces cerevisiae* [48, 49]. Also like other TADS [50], this region of MYC is a potent “degron” [51] and is the primary domain responsible for signaling the rapid destruction of MYC by ubiquitin- (Ub-) mediated proteolysis [52].

It is interesting to note that although full-length MYC is a notoriously weak activator of pol II genes [53], the TAD itself, when fused to a heterologous DBD, is exceptionally potent—comparable in magnitude to the canonical VP16 activation domain [45, 54]. Although the apparent strength of the isolated MYC TAD could be due to peculiarities of the assay systems involved, these assays do faithfully reflect differences between the C- and L-MYC TADs that underlie their different tumorigenic potentials [33], making it difficult to dismiss the results as entirely artifactual. One possibility is that processes operate within full-length MYC to temper its transactivation potential, allowing for bursts of MYC activity at specific points in development or in response to specific signals but otherwise keeping its activity in check. The ability of cells to tightly limit MYC expression and activity is a recurring theme in MYC biology and one that we will return to later in this review.

At the carboxy terminus of MYC is a ~100 amino acid basic helix-loop-helix-leucine zipper (BR-HLH-LZ) region that functions as its DNA-binding domain [55, 56]. This type of DNA binding domain is not unique to MYC but is found in other sequence-specific transcriptional regulators including the Pho4 activator in yeast [57] and the hypoxia-inducible HIF-1 α factor in mammalian cells [58]. BR-HLH-LZ proteins bind DNA as obligate dimers and recognize a consensus sequence “CACGTG,” which is termed the “Enhancer box” (E-box) [59]. At physiological concentrations, MYC does not homodimerize [56] but instead interacts with the small BR-HLH-LZ protein MAX to form a heterodimer that constitutes a core DNA-binding module [60]. Dimerization of MYC with MAX is driven by the leucine zipper which forms an extended

FIGURE 3: Crystal structure of a MYC/MAX heterodimer bound to a canonical E-box. Only the structure of the BR-HLH-LZ region was solved [1]. Details are described in the main text.

coiled coil between the two proteins [1] (Figure 3) that, following a crisp turn at the loop, presents two basic helices that insert into the major groove of the DNA in scissor-like fashion. Interaction of MYC with MAX occurs at all MYC-bound genes across the genome [61], is absolutely required for MYC's oncogenicity [62, 63], and is an important point of MYC regulation, as MAX dimerizes with additional BR-HLH-LZ proteins that antagonize the MYC-MAX interaction [38].

In contrast to the two extremes of MYC, the “central portion” of the protein is poorly understood, due in large part to functional redundancies and lack of consistency in the behavior of central portion MYC mutants. For example, this segment contains a potent nuclear localization signal (NLS) that is nonetheless dispensable for entry of c-MYC into the nucleus [64] and is entirely missing from the L-MYC protein, despite the latter's profoundly nuclear localization [65]. Additionally, deletion mutations within this region have failed to identify elements that are consistently required for MYC activity, with select mutants being functional in some assays of transformation but not others [46, 66, 67]. It is important to note, however, that the central portion of MYC does contain a number of highly conserved sequences that contribute to its function (see below) and, as early studies often used nondirected mutants and failed to account for differences in MYC protein expression, it is very likely that a more systematic analysis of the central portion of MYC could yield important new information about its mechanisms of action.

3.2. Conserved MYC Sequences: Thinking Inside the Box. As well as traditional structure-function analyses, insights into critical regions of the MYC protein have been gleaned by analysis of conserved segments within the proteins, termed “Myc boxes” (Mb) [68]. Alignment of MYC family members across species reveals large regions of poor to moderate conservation that are punctuated by six islands of frank homology: five MYC boxes—MbI, MbII, MbIIIa, MbIIIb, and MbIV—and the BR-HLH-LZ motif (Figure 2). The conservation of these elements suggests that they serve critical functions, and—where examined—this notion is borne out by experimental evidence. Myc box I lies within the TAD and is required for cellular transformation in some contexts but not others [46, 69]. It is a primary point of contact of MYC with p-TEFb [70, 71], a cyclin-CDK complex that phosphorylates RNA polymerase II, stimulating transcriptional elongation and coordinating transcription with events of pre-messenger RNA processing [72]. Beyond its role in the transcriptional functions of MYC, MbI also hosts a set of hierarchical phosphorylation events [73] that create a binding site for the SCF^{Fbw7} Ub-ligase [74–76], a regulator of MYC protein stability. Interestingly, and as discussed later, MbI is also a hotspot for accumulation of mutations in Burkitt's lymphoma [77–81], several of which stabilize the MYC protein [52] and render it profoundly oncogenic in mouse models of lymphomagenesis [82].

The most well-studied Myc box, as well as one considered “ground zero” in terms of MYC function, is MbII. Seated within the TAD, Myc box II is essential for the ability of MYC to promote cellular transformation *in vitro* [46], to drive tumorigenesis *in vivo* [82], and to activate [83] and repress [69, 84] transcription of the majority of MYC target genes. Critical to the function of MbII is its interaction with the coactivator TRRAP [85], which recruits a histone acetyltransferase (HAT) complex [86, 87] that acetylates histone H4, thereby opening chromatin structure and promoting transcription at MYC-bound genes [87, 88]. MbII is also important for precise regulation of the MYC protein; it contributes to MYC degradation [89, 90], integrates MYC activity with the health of ribosome biogenesis via competitive binding of TRRAP with the ribosomal L11 protein [91], and has been proposed to rein in MYC function by interacting with the SCF^{Skp2} Ub-ligase [92, 93], thereby committing MYC to a mode of transcriptional activation that will obligatorily lead to its destruction [94].

In contrast to MbI and II, much less is known about the other Myc boxes. Myc box IIIa (often referred to as simply “MbIII” [69, 90]) is required for transformation by MYC *in vitro* [69] and for full tumorigenicity *in vivo* [69]. It participates in MYC destruction by the Ub-proteasome system [90]. And it contributes to transcriptional repression by MYC via recruitment of a histone deacetylase, HDAC3 [95], a process that accelerates oncogenesis by inhibiting the expression of the tumor-suppressive microRNA (miRNA) miR-29 [96]. Interestingly, L-MYC proteins do not possess MbIIIa (Figure 2), but whether this plays a part in their reduced oncogenic potential [32, 33]—or indeed whether MbIIIa

FIGURE 4: Restricting MYC expression and activity. Each stage in MYC expression, from transcription of the MYC gene through to a functionally active MYC protein, are presented in terms of the central dogma. Events that control or suppress these stages are indicated by red boxes. Many of these processes are perturbed in cancer. See text for details. TXN, transcription; TLN, translation; PTMs, post-translational modifications.

has other functions and binding partners besides HDAC3—remains to be determined.

Myc box IIIB has not, to my knowledge, been systematically studied in any mammalian system; a remarkable oversight given its presence in every earthly MYC protein.

Finally, Myc box IV has been studied in just one publication [97]. It is required for the full proapoptotic functions of MYC but not its ability to induce cell proliferation, and it contributes to both transcriptional activation and repression of MYC target genes. Despite lying outside of the BR-HLH-LZ, deletion of MbIV renders MYC less able to bind DNA both *in vitro* and in cells, suggesting that it somehow contributes to target gene recognition. It is not known whether this effect is due to MbIV making contact with DNA, or recruiting additional factors, or whether deletion of this element perturbs structural aspects of MYC that prevent efficient binding by MYC/MAX heterodimers.

3.3. Is the Map of MYC Complete? Given the volume of work on the subject, one might expect that we understand the contribution of almost every amino acid within MYC to its functions as a transcriptional regulator and oncoprotein. And yet, except for the two extremes of the protein, this is not the case. The central portion of MYC is largely uncharted territory, particularly with respect to Myc boxes IIIa, IIIB, and IV. The conservation of these elements implies an important common role and leads to the notion that they must be involved in protein-protein (or perhaps protein-DNA) interactions critical to the intrinsic functions of MYC. As the search for new ways to target MYC in cancer accelerates, uncovering the function of these elements seems fertile territory that could lead to new therapeutic routes of intervention. Additionally, beyond Myc boxes, we know very little about the segments in MYC that are not universally conserved across MYC proteins but are conserved within individual members of the MYC family. The payoff for understanding the function of these sequences could be tremendous. For example, learning how

sequences unique to L-MYC contribute to small cell lung cancers could very well lead to insight into unique oncogenic processes that occur within that specific tumor environment and lead to development of therapies that are more effective and induce less collateral damage on other cell and tissue types. It may not be the most glamorous work, but more careful investigation into how the entire sequence of MYC proteins dictates their function is one major gap that needs to be filled in the MYC arena.

4. Mechanisms of MYC Regulation and Its Deregulation in Cancer

A little bit of MYC is a good thing. Normal fibroblasts in culture typically express just a few thousand molecules of MYC protein per cell [98], yet this can be over two orders of magnitude higher in cancer cell lines growing under similar conditions [61]. Before reviewing the broad impact of increased MYC burden on cellular processes, it is worth discussing how normal cells control MYC and how these processes go awry in cancer.

4.1. Regulating MYC: Just Say “No”. One important principle to emerge from studies over the last 30 years is that mammalian cells have evolved a sophisticated network of processes that constantly impede MYC action. Indeed, if one considers MYC expression and activity in terms of the central dogma (Figure 4), it is clear that MYC proteins are subject to some kind of stringent control at every step of their life. A primary point of regulating MYC is at the level of transcription. MYC is an “immediate early” gene [99]—not transcribed in quiescent cells but rapidly induced in response to growth factor signaling [100, 101]. Regulation of MYC transcription is exerted at both the level of initiation [102] and of release of paused RNA polymerase II [103, 104] and integrates both positive and negative inputs to insure that MYC genes are transcribed only in the presence of

appropriate “go” signals within the cellular milieu. Following transcription, the MYC mRNA itself is subject to several restrictive processes that are also tuned to the growth status of the cell. Export of MYC mRNA to the cytoplasm is coordinated by the translation initiation factor eIF4E [105], which is under direct control by mitogenic signals [106] and binds the MYC message early during the transcription process, leaving little chance that errant MYC mRNAs can escape the nucleus without appropriate restraint. Once in the cytoplasm, translation of the MYC mRNA is suppressed by factors that mediate productive ribosome engagement [107] and is temporally limited by the extraordinarily short half-life of the mRNA [108]. And following synthesis, the protein itself is under intense scrutiny and control. MYC is subject to a bevy of posttranslational modifications that include phosphorylation, acetylation, glycosylation, and ubiquitylation [109–111], many of which interact to establish particular states of MYC expression or activity. The ubiquitylation of MYC, in particular, appears to be an important point of control [112]. Not only is the rapid Ub-mediated proteolysis of MYC crucial for keeping MYC levels low and tied to early processes that restrict MYC synthesis, but ubiquitylation of MYC—as well as its deubiquitylation [113, 114]—acts to modulate the inherent transcriptional properties of the protein [92, 93, 115, 116], providing a “point of action” mode of control that micromanages MYC activity. Finally, MYC activity is also restricted by the action of specific proteins mentioned above that either interact directly with MYC to limit its function [91] or interact with MAX to prevent MYC from finding its essential partner protein [38].

Much in the same way as multilayered systems are in place to allow nuclear reactors to safely harness the power of nuclear fission, the processes that restrict MYC conspire to allow cells to efficiently manage its function for their normal activities without stepping on the path to tumorigenesis. As discussed below, however, and analogous to a nuclear meltdown, failure of these processes at any point can have catastrophic outcomes.

4.2. MYC Deregulation in Cancer. One of the key concepts in understanding how MYC is deregulated in cancer is the fact that—unlike oncoproteins such as RAS [117]—the coding sequence of MYC does not *need* to be changed in order for its oncogenic potential to be unleashed. As discussed in the next section, mutant forms of MYC are prevalent in Burkitt’s lymphoma but are not widely seen in other cancers, and all evidence from cell- and animal-based studies is that expression of a pristine form of MYC is sufficient to promote tumorigenesis [24, 118–121]. The most common route to a MYC-driven cancer, therefore, is changes that lead to overexpression of MYC and disconnect it from the critical signaling processes (above) that normally keep it in check.

On average, 50% of human cancers show increased expression of MYC (for a comprehensive presentation of the statistics, see [122]), a characteristic that usually correlates with poor patient survival [101]. The percentage of cancers functionally overexpressing MYC is certainly much higher, as most studies to date have focused on MYC gene and RNA

dosage, which are invisible to perturbations that increase the synthesis of MYC proteins or slow their rate of degradation, and do not account for functional deregulation of the protein. Although the range of cancers prompted by individual MYC proteins is fairly well delineated (Section 3), the MYC family as a whole are equal opportunity oncoproteins and are overexpressed in cancers as diverse as lymphoma, melanoma, multiple myeloma, and neuroblastoma, as well as colon, breast, and lung cancers [39, 122]. It is these statistics that give MYC its formidable reputation but also inspire researchers with the promise that therapeutic strategies to target MYC could have broad impact in reducing or eliminating many cancer fatalities.

There are many interesting ways in which cancer cells deregulate MYC, but they typically fall into one of two categories: changes to the MYC loci themselves that stimulate increased MYC mRNA production, or changes extrinsic to MYC that disarm critical regulatory mechanisms. As mentioned early in this review, retroviral promoter insertion was the first mechanism recognized to lead to enhanced MYC transcription [20–22] and was a seminal discovery in terms of cementing the role of MYC as a *bona fide* oncogene. This was soon followed by the observation that the *c-MYC* locus is translocated in Burkitt’s lymphomas and mouse plasmacytomas [123, 124], an event that places MYC coding sequences under the control of the immunoglobulin μ heavy chain enhancer, driving very high levels of mRNA synthesis. This translocation, as well as others of similar nature, are found in 100% of Burkitt’s lymphoma patients and indeed are used (together with other approaches) to diagnose the disease [125].

Despite their prevalence in Burkitt’s lymphoma, such rearrangements are not common in other cancers, where the typical mode of increasing MYC synthesis via genomic modification is gene amplification [122]. This manner of MYC induction is fairly common in cancer, affects all MYC family members, and can take the form of small focal amplifications [126, 127], large amplifications [128], and double-minute chromosomes [129]. Although increasing the number of copies of MYC does not always correlate with MYC overexpression [130, 131], the frequency with which MYC gene amplification occurs and the correlation of this event with metastatic disease and poor prognosis [132] strongly indicate a direct role for MYC gene amplification in many human malignancies.

It is important to note that MYC mRNA synthesis can also be affected by genomic changes that, at first blush, have little to do with the MYC gene itself. An inherited nucleotide variant, rs6983267, was recently described as conferring increased risk to colorectal and prostate cancer [133]. Subsequent studies showed that—although this polymorphism occurs more than one megabase away from the *c-MYC* gene—its tumor-promoting properties manifest by stimulating binding of the TCF-4 activator to a previously unrecognized distal MYC enhancer, thereby leading to increased MYC transcription [134, 135]. The remoteness of this enhancer from the MYC gene raises the distinct possibility that other, apparently unconnected, genomic changes that occur in cancer could result in increased MYC transcription.

FIGURE 5: Frequency and location of lymphoma-associated point mutations in *c-MYC*. The histogram shows the number of times that independent point mutations altering the coding sequence of *c-MYC* have been reported in the literature, isolated from either patient samples or cultured cell lines. Duplicate identifications (e.g., those occurring in the same cell line but reported by different investigators) have been removed. The analysis did not differentiate between conservative and nonconservative amino acid changes. The histogram is fit to scale atop a cartoon of MYC, showing conserved sequences, functional elements, and regions involved in controlling the metabolic stability of the protein.

External to MYC, it is reasonable to assume that any of the processes depicted in Figure 4 could be subject to deregulation in tumor cells. Indeed, uncovering which events are frequently perturbed in tumors provides valuable insight into those mechanisms that are most important for the normal control of MYC. A few prominent examples illustrate the diversity of ways MYC can run amok in cancer cells. At the level of transcription, it is clear that *MYC* lies at the end of a set of signal transduction pathways that become ectopically activated in cancer. Loss of the adenomatous polyposis coli (*APC*) tumor suppressor, for example, which occurs in almost all colorectal cancers [136], leads to the accumulation of β -catenin, which in turn binds to the TCF-4 activator (mentioned above) to stimulate constitutive and high-level transcription of MYC [137]. Similar scenarios result in potent induction of MYC transcription in response to perturbations of Sonic hedgehog [138] and Notch signaling pathways [139, 140]. At the level of mRNA dynamics, stability of the MYC message can be increased in cancer cells [141]. And the eIF4E translation factor that exports MYC mRNA from the nucleus is overexpressed in a slew of malignancies [106], functioning as an oncogene by stimulating the translation of a cohort of growth-promoting factors, including MYC [142]. Finally, at the level of protein destruction, MYC can be stabilized by viral oncogenes [143] and by loss of critical regulators such as the SCF^{Fbw7} ubiquitin ligase [144] that is inactivated in an estimated 6% of all human cancers [145]. Given the plethora of ways that tumor cells can increase their MYC burden, it is not unrealistic to conclude that loss of appropriate control over MYC contributes in a substantive way to all malignancies.

4.3. MYC Mutations in Cancer. Tumor-associated mutations that alter the *c-MYC* coding sequence were reported as early as 1983 [77] but have received surprisingly little attention in the last 30 years—and not without reason. Such mutations are found in a very narrow spectrum of tumors—principally Burkitt's lymphoma and a smattering of AIDS-associated

hematologic malignancies [78–82, 146–151]—and are always associated with some other genomic rearrangement that itself leads to a massive increase in MYC expression, such as translocation proximal to the immunoglobulin μ enhancer. As such rearrangements are clearly sufficient to drive lymphomagenesis independent of any changes in the MYC protein, the likelihood that these mutations contribute meaningfully to the pathophysiology of the disease is small. Moreover, because the translocated MYC allele is placed within a hypermutable region of the genome [152], it is tempting to view these mutations as “collateral damage” and noninformative to understand MYC function in this setting.

Nonetheless, changes to the coding sequence of MYC are found in nearly 50% of Burkitt's lymphomas [78] and cluster in specific and recurring places on the protein (Figure 5), suggesting that they are not neutral events. And, where examined, these mutations do impact MYC regulation and function. A common theme in this area is that tumor-derived mutations subvert the rapid destruction of MYC by Ub-mediated proteolysis. As shown in Figure 5, these mutations typically cluster within elements that control MYC stability—the TAD/degron [52], the “D-region” [90], and the “PEST element” [153] (for review of these elements see [112])—and several of the most common recurring mutations have been shown to stabilize MYC in cultured cells [52]. Indeed, the most frequently mutated residue in the tumor collection is threonine 58 (T58), which lies within the heart of the phosphodegron that is recognized by SCF^{Fbw7} to promote MYC destruction [74–76]. The fact that the MYC—SCF^{Fbw7} interaction is disturbed in *trans* by loss of Fbw7 [144] and in *cis* by recurring tumor-associated MYC mutations [52] provides compelling support for the idea that breaking Ub-mediated turnover of MYC is advantageous to cancer cells.

The impact of tumor-derived mutations on MYC function has been controversial. Early reports indicated that mutations within Mbi (e.g., T58A) disrupt interaction of MYC with the Rb family member p107 [154, 155], but it remains unclear whether p107 is a physiologically relevant

MYC partner protein. Moreover, it is difficult to tease apart direct effects on MYC function from effects that occur as a result of increasing MYC protein levels. The T58A mutation increases the transforming ability of MYC *in vitro* [156, 157] and renders MYC aggressively oncogenic in mouse systems of lymphomagenesis [82] and mammary cancer [158], as might be expected from a perturbation that increases MYC protein expression. What is curious, however, is that the T58A mutant protein achieves its enhanced tumorigenic activity by selectively disabling the proapoptotic function of MYC [82, 156], a remarkable feat given that enhanced MYC burden is associated with increased apoptotic potential [159]. One possibility is that mutations such as those at T58 not only disturb the levels of MYC but also *qualitatively* alter its function, either by disrupting an entirely different process or by perturbing its normal patterns of ubiquitylation, which are known to modulate MYC activity through both proteolytic and nonproteolytic means [92, 93, 115, 160, 161]. Further investigation will be required to fully understand the impact of these mutations on MYC.

4.4. Losing Control of MYC: Is There More to Learn? Reflecting on the history of MYC, it is astounding to see that a basic tenet of the MYC field—that enhanced MYC expression leads to cancer—was articulated in the very earliest days of MYC research [21]. Over the intervening years, we have certainly come to appreciate the myriad of ways this can occur, but that fundamental concept has not changed. With so much effort already having been spent on understanding how MYC is deregulated in cancer, is there any more valuable information to be learned from continuing to study this aspect of MYC biology?

Understanding how cancer cells lose control of MYC and when this occurs in the process of disease progression is immensely important in terms of staging cancers, predicting outcomes, and designing therapies. In the emerging world of “precision medicine” [162], matching the molecular cause with the pharmacological cure is paramount, meaning that if MYC expression is to be targeted we need to know the basis and significance of elevated MYC levels in each patient. Outside of gene amplification and translocations, however, this can be challenging. The increasingly powerful genomic approaches used to interrogate tumor cells hold great potential for unlocking common transcriptional pathways, mutations, and epigenetic changes that lead to ectopic MYC production in each cancer type but will need to be married with functional studies to dissect underlying mechanisms and contributions to oncogenesis. The relatively recent discovery of the distal MYC enhancer discussed above, for example, illustrates how much we have to learn about just one aspect of MYC regulation. And recurring tumor-derived mutations in MYC are a neglected area, with only a handful of mutants being analyzed and key questions remaining as to how these mutations truly impact tumorigenesis. Given all that has been learned about important tumor molecules such as APC, RAS, p53, and VHL from studying their tumor-associated mutations, it seems that our understanding of MYC would benefit from taking advantage of cancer’s ability to shine a spotlight on critical regulatory processes.

5. Tumor-Relevant Actions of MYC

What does MYC do to cells that pushes them on the path to tumorigenesis? As described in Section 6, MYC almost certainly acts by regulating the expression of genes that promote transformation, but there is still considerable controversy over precisely which genes are important, the role of transcriptional activation versus repression, and how the modest transcriptional output of MYC [53] leads to such dramatic changes in cell behavior. Before delving into the molecular processes that lie at the heart of MYC’s oncogenic activity, therefore, it is useful to step back and examine the phenotypic consequences of ectopic MYC function on the cell. The overarching theme here is that MYC takes a holistic approach towards transformation by modulating a broad range of cellular events relevant to tumorigenesis (Figure 6). Below I discuss several of the more high-profile and illuminating consequences of unrestrained MYC activity on cell comportment. Note that although these consequences are discussed separately, there is likely to be significant overlap in the molecular events that contribute to each of these outcomes and significant interactions between them.

5.1. Pushing the Cell Cycle. MYC proteins are not classic cell-cycle regulators, in that their expression or function is not typically modulated during the course of a normal cell cycle [163–165]. MYC proteins do, however, profoundly influence the capacity of cells to enter the cell cycle, as well as accelerating the rate of key stages in cell cycle progression. As mentioned, MYC is an immediate early gene that is one of the first to be induced upon exposure of quiescent cells to growth factors [99] and in fact is required for a robust cell cycle response to mitogenic signals [166, 167]. MYC also expedites both the G1 and G2 phases of the cell cycle [166, 168, 169], causing cells to cycle more rapidly, and have reduced requirements for growth factors to maintain the cycling state. Most notable, however, are findings that forced MYC expression is *sufficient* to drive quiescent cells to re-enter the cell cycle [170, 171], independent of any growth stimuli. Direct activation of cyclin/CDK expression and inhibition of cell cycle checkpoints [172] appear to be the mechanism through which MYC works in this capacity. The ability of MYC to take a cell that has responded to the lack of mitogens appropriately and exited the cycle and force that cell to replicate is undoubtedly one of its most prominent tumorigenic actions.

5.2. Apoptosis, a Key Tumor-Defense Mechanism. In the absence of survival factors, forced expression of high levels of MYC in otherwise normal cells promotes apoptosis [25, 26]—a process by which cells rapidly and systematically deconstruct their internal anatomy prior to engulfment by their neighbors [173]. It may seem antithetical to discuss apoptosis among the list of tumor-relevant MYC activities, but the ability of MYC to drive programmed cell death is one of the important integrated safeguards to prevent tumorigenesis and one that must almost always be subverted for a MYC-overexpressing cell to become cancerous. Indeed, the ability of oncogenes such as MYC to promote apoptosis

FIGURE 6: Key tumor-relevant functions of MYC proteins. The cartoon illustrates five of the most high-profile tumor relevant processes that are influenced by ectopic MYC expression. This image reflects an aggregate of MYC activities, and is not meant to imply that all functions necessary contribute to any one specific cancer setting.

and the need for this process to be overcome in cancer underlies the phenomenon of oncogene cooperation [24] and the now familiar concept that multiple genetic perturbations are required for tumor development [174]. Apoptosis is also a key to understanding the action of chemotherapy agents and the acquisition of chemotherapy resistance [175], and as a result much effort has been spent on unraveling how MYC triggers this process.

Like many oncogenes [176], MYC proteins induce apoptosis through a number of mechanisms, some of which are dependent on cellular context. MYC can function by disturbing the equilibrium between pro- and antiapoptotic proteins, particularly those in the BCL-2/BH3-only category [177]. During lymphomagenesis, for example, MYC suppresses expression of the antiapoptotic Bcl-2 and Bcl-X(L) proteins [178], while at the same time stimulating expression of the proapoptotic BH3-only protein (and Bcl-2 antagonist) Bim [82, 179], thereby priming the mitochondria for cytochrome c release and induction of the apoptotic program [177]. MYC can also act directly on the same process by activating Bax [180], the mitochondrial protein responsible for inducing the events that lead to caspase activation. And MYC can promote apoptosis by inducing the expression of other proteins that themselves trigger apoptotic tumor-defense mechanisms,

such as the E2F family of transcriptional regulators [181]. By far and away the most pervasive process through which MYC induces apoptosis, however, is via the ARF-MDM2-p53 axis [182]. In this scenario, MYC increases expression of the ARF tumor suppressor [183], which in turn destabilizes and inactivates the MDM2 Ub-ligase [184–186], thereby leading a rapid induction of p53 and activation of its broad tumor-suppressive apoptotic response [187]. Interestingly, ARF also binds directly to MYC [188], a process that both redirects MYC to activate novel proapoptotic genes [161] and stabilizes the ARF protein [189], the latter of which has been suggested to be an important mechanism through which cells discriminate between low (normal) and high (oncogenic) levels of MYC. The role of ARF-MDM2-p53-mediated apoptosis in combatting the tumorigenic potential of MYC is reflected in the frequent loss of p53 in human cancers [190] and evidenced by data from mouse model systems showing that loss of this pathway collaborates with MYC to drive oncogenesis [191, 192] and that certain tumor-derived mutations in MYC that prevent it from tripping p53-dependent tumor surveillance mechanisms (e.g., T58A) are profoundly oncogenic [82].

5.3. Cell Growth and Metabolism. Rapidly dividing cells need a steady stream of nutrients, energy, and proteins to sustain

a high rate of duplication and division. Given the capacity of MYC to promote cell cycle progression, it is perhaps not surprising that its signals to the cell to “go” are backed up by an impressive array of growth-promoting properties that fuel cell expansion.

It was recognized as early as the mid-1990s that MYC stimulates cell growth—the accumulation of cell mass by enhanced protein synthesis [193]. Cells forcibly expressing MYC grow to twice the size [194], make twice as many proteins [194], and carry twice the total RNA content [61, 195] of comparable cells with normal MYC levels. As seen throughout this review, MYC achieves this feat through a massively parallel set of activities that, in this case, target just about every step in protein catabolism. MYC broadly activates the expression of protein-coding genes involved in ribosome biogenesis [196, 197] and protein translation [198] and can stimulate translation of individual mRNAs by promoting their capping [199]. In addition to these processes, MYC also increases the translational capacity of cells by activating transcription by RNA polymerases I [200, 201] and III [202], which increases synthesis of rRNAs and tRNAs, respectively. And MYC collaborates with mTOR—the master regulator of protein synthesis—to directly stimulate the activity of factors (notably an eIF4E-binding protein) that ramp up the efficiency with which mRNAs productively engage the ribosome [203]. The importance of enhanced protein synthesis to MYC function is dramatically demonstrated by the finding that reducing the number of ribosomes in a precancerous cell overexpressing MYC is sufficient to suppress the transition of that cell to the tumorigenic state [204].

Hand in hand with its electrification of protein synthesis, MYC also intensifies and reprograms the metabolic capacity of cells to support their rapid expansion (for review see [205]). Although there are many ways this occurs, two of the most illustrative are by inducing changes in glycolysis and changes in glutamine metabolism. It has been known for almost 90 years that cancer cells typically display enhanced glycolysis and glucose utilization [206] and that this metabolic reprogramming offers a set of advantages to tumor cells, helping them grow, invade, and survive under conditions of wavering oxygen tension [206]. MYC stimulates the expression of a broad set of genes involved in glucose uptake and glycolysis [207], and key glycolytic regulators such as LDH-A are activated by MYC in a variety of cell types [208]. Moreover, cells transformed by MYC become “glucose addicts,” rapidly undergoing apoptosis in response to glucose deprivation or exposure to glucose antimetabolites [209]. In a similar vein, MYC-transformed cells also have a profound appetite for glutamine and enhanced glutamine metabolism [210], again mediated by MYC-driven changes in the expression of key metabolic enzymes [210, 211] and again converting cells to a state in which they become addicted to glutamine for their survival [211]. The sweeping changes that MYC implements to cellular metabolic processes and the requirement of each of these changes for tumor cell persistence has generated considerable excitement over the prospect that metabolic inhibitors could hold the key to selective destruction of cancer cells in the clinic [206].

5.4. Genomic Instability. Changes to the genetic makeup of a cell are the fuel that drives the onset and progression of tumorigenesis. It is clear that aberrant proliferation induced by oncogenes disconnects the events of DNA replication from other processes that must normally be tightly coordinated to insure faithful chromosome duplication. This process results in (among other things) a phenomenon termed “replication stress” [212]—the collapse of DNA replication forks at fragile sites in the genome [213] that, when resolved, leads to double-stranded DNA breaks, loss of heterozygosity, and other abnormalities. MYC is no exception here [214]. The effects of MYC on DNA replication were noted as early as 1987 [215], and within a few years it became apparent that MYC promotes amplifications and rearrangements at select loci [216] and induces genome-wide chromosomal abnormalities [217]. Forced expression of MYC induces DNA damage [218], likely via induction of harmful reactive oxygen species (ROS; [218, 219]), although ROS-independent, MYC-driven DNA breaks have also been reported [220]. MYC also triggers premature origin firing and disrupts the symmetry of the DNA replication fork [221], leading directly to fork collapse and its resultant impact on DNA integrity. Finally, MYC acts to uncouple the events of S-phase from those that occur in mitosis [222], causing endoreduplication and thus aneuploidy [222, 223].

The effects of MYC on genomic integrity is intuitively aligned with our thinking of how cancer cells evolve. There was some initial skepticism as to whether the effects of MYC on DNA replicative processes were important for its tumorigenic functions, or indeed whether ongoing genomic instability occurs in cancer and truly drives progression of the disease [224]. It should be noted, however, that replicative stress at least is now generally recognized as a common and relevant oncogene function [212], and it is hard to imagine how the impact of MYC on genomic integrity *could not* contribute in some way to cancer onset or progression. Interestingly, the actions of MYC on genome maintenance may very well be one place where nontranscriptional mechanisms are at work, and we shall return to discuss these possible mechanisms and their consequences in Section 7.

5.5. Influencing the Tumor Environment. Although MYC first surfaced within the context of blood-borne cancers, it is clear that MYC is a common driver of solid tumors, where the challenges of forming a “malignant organ” [225] demand a blood supply and extensive interactions with the surrounding extracellular matrix and connective tissue. To wreak havoc, malignant tumors must also escape their primary site and metastasize, an event of extreme clinical significance because it leads to over 90% of all cancer fatalities [226]. MYC meets these demands in several ways. MYC increases expression of vascular endothelial growth factor [227] and decreases the expression of thrombospondin-1 [228] to trip the “angiogenic switch”—that point in tumor development where events align to allow nascent tumor masses to develop their own vasculature. MYC protein stability is fine-tuned to allow tumor cells that are distant from the nutrient and oxygen supply of blood vessels to decrease their MYC levels, avoiding the inevitable death that would occur as a result of nutrient deficiency in the

core of the tumor mass [229]. In models of pancreatic cancer development, forced expression of MYC in β -cells leads to release of the inflammatory cytokine interleukin- β , which in turn coaxes adjacent endothelial cells to proliferate and form the vascular network [230], a function further stimulated by MYC-dependent activation of inflammatory responses that lead to stromal remodeling [231]. And finally, MYC also appears to play both direct and indirect roles in inducing tumor metastasis. Indirectly, the effects of MYC on angiogenesis could certainly promote metastasis, as hematologic spread is a significant mechanism for transportation of tumor cells to distant tissues. This process could also be facilitated by the ability of MYC to promote cell “stemness” [28, 232, 233], which in turn leaves migrated cells in a better state to thrive in distal, foreign, tissues. Directly, MYC stimulates the expression of factors that enhance tumor invasion [234] and reduce cell adhesion [235], and regulates key micro-RNAs to promote the epithelial mesenchymal transition [236–238]. As the switch of polarized epithelial cells to the motile mesenchymal phenotype is recognized as a major contributor to tumor invasion and metastasis [239], the ability of MYC to tap into this process arguably contributes to the all-too-frequent poor prognoses of cancer patients with frank MYC overexpression [132].

5.6. Will the Real Mechanism of Tumorigenesis by MYC Please Stand-Up? Because of its impressive array of functions connected to cancer onset and progression, MYC has been dubbed “the oncogene from hell” [224]. And it is certainly true that each of the activities described here (and others) impinge on the very fundamental characteristics that define cancer [240]. With so many ways that MYC *can* drive cancer at its disposal, which is most important? Are all of these functions required, or are some less relevant than others?

Across the entire spectrum of all human malignancy, it is easy to imagine how each of these functions of MYC could contribute to either the initiation, maintenance, or progression of the tumorigenic state. But for individual cancers, which evolve from distinct cell types in specific niches, it is likely that not all of the tumorigenic functions of MYC operate or even confer an advantage to individual cancer cells. In considering the relationship of these activities to human malignancy, it is important to remember that few, if any, studies have examined whether the MYC activities described here manifest simultaneously, influence distinct phases in tumor progression, or are restricted by cell identity or environment or even the mechanism with which MYC expression is activated. And recall that most of what we know about MYC comes either from cells grown in tissue culture or from mouse models in which cancers are driven under rarefied conditions where MYC is manipulated to be the primary oncogenic lesion. Understanding how all of these functions apply to the complex equation of spontaneous human tumors is a key question that will require development of more complex models that better mimic human disease.

In a somewhat counterintuitive way, the vast array of pro-tumorigenic functions of MYC may actually be beneficial to design of effective ways to treat cancers where MYC is

induced. One of the recurring themes in this arena is that, in model systems at least, many of the individual functions of MYC are each required for tumor maintenance. Cancer cells are highly dysfunctional and achieve that state by pushing the processes of growth, proliferation, metabolism, and cell architecture to their limits. As such, cancer cells are more likely to be susceptible to perturbations that restrain any one of these processes than normal cells that tend to “buffer” their critical functions. In therapeutic terms, therefore, it may not matter which MYC-driven process is more important to tumorigenesis but rather which is more amenable to selective inhibition in specific cancer cell types.

6. Transcriptional Functions of MYC

Reflecting on the history of MYC research, it is interesting to see how views on its function as a transcriptional regulator have evolved. After the discovery of MAX [60] and definition of its transcriptional activation domain [33, 45], the hunt was on for discovering “the” critical target genes that are activated by MYC [241, 242]. As MYC was interrogated in more detail, the number of MYC target genes expanded dramatically (into many thousands; [243–245]), MYC was shown to have repressive as well as stimulatory roles in transcriptional regulation [246], and eventually the concept emerged that MYC controls the expression of *every* active gene in a given cell type [61, 195]. Because this area is still evolving and a consensus view is yet to emerge, I will discuss some of the challenges in understanding the transcriptional properties of MYC, highlight common themes in this area, and share some hope on what future years of research in this field may bring.

6.1. Defining MYC Target Genes. Conceptually, defining a target gene for any transcription factor should be a fairly straightforward exercise. Important criteria include the presence of that factor’s cognate DNA binding sequence in critical regulatory elements within a gene, the physical association of the transcription factor with those segments *in vivo*, and a change in the transcriptional output of the gene in response to the appearance, or disappearance, of the factor. Once these criteria are satisfied on a genome-wide scale, a “transcriptional signature” can be developed that allows for inference of the impact of that factor on transcriptional events within a given cell, which in turn can be used for purposes of diagnosis of disease states, or dissection of downstream mechanisms that exert the physiological actions of that factor. For MYC, however, this process has not been easy, and it is still difficult to make definitive statements about sets of genes that are directly controlled by MYC across all cell and cancer types [247] and that are central to its oncogenic properties. The reasons that have stymied this undertaking, however, are almost as informative as the results of the studies themselves and provide a useful framework for analyzing the action of MYC in gene regulation, particularly the ways it selects target sites in the genome (Figure 7).

First, canonical E-boxes are prevalent throughout the genome, occurring on average once every 4 kb [248]. Moreover, MYC/MAX dimers are also able to bind degenerate E-boxes [61] and to promoters bereft of this element [249–252],

FIGURE 7: Targeting MYC to chromatin. The figure shows four ways that MYC can be targeted to its genomic sites *in vivo*. (a) *The classic view*. In this model, binding of MYC/MAX dimers to DNA is signaled primarily through sequence-specific recognition of the E-box by the BR-HLH-LZ regions of each protein (Figure 4). (b) *Effect of chromatin context*. In this model, MYC/MAX dimers will only bind E-boxes within a permissive chromatin environment, marked by the presence of CpG islands and active histone modifications such as H3-K4 methylation (me). (c) *Effect of MYC dosage*. At low levels of MYC (top panel), MYC/MAX dimers bind primarily to promoter proximal canonical E-boxes. At high levels of MYC, MYC/MAX dimers bind E-boxes at distal enhancer sequences and also recognize imperfect E-box sequences (“iE”). (d) *Recruitment by other transcription factors*. In this image, MYC/MAX dimers are recruited by the retinoic acid receptor- α (RAR) to its cognate DNA element (RARE) to regulate entirely new sets of genes. Note that interaction with RAR α does not account for all or likely most of the E-box independent binding of MYC that has been reported. Also note that these mechanisms are not mutually exclusive.

and it is important to recall that E-boxes themselves bind not just MYC, but also an entire set of other BR-HLH-LZ proteins [59]. The frequency with which E-boxes occur and the ability of MYC to bind chromatin in their absence make it difficult to predict whether any gene will functionally respond to MYC simply by inspection of its primary DNA sequence. And examining MYC binding by techniques such as ChIP-seq may not help either, as these approaches typically show a pervasive level of interaction of MYC across thousands of sites on chromatin [61, 195, 243–245], with no robust way to

assess a functional outcome. Placing MYC at “the scene of the crime,” therefore, may not be stringent-enough criteria, especially considering that MYC activates typical reporter gene constructs only weakly [242], meaning that one of the past gold standards for establishing a transcription factor–target gene relationship—a requirement for the presence of the cognate *cis*-DNA element for transcriptional response [253]—is rarely met for MYC.

Second, binding of MYC to sites on chromatin is not simply dependent on the presence of an E-box or other specific DNA sequences. The impact of genomic approaches to resolving not only the global binding of MYC but also its correlation with a host of chromatin characteristics has revealed that MYC has a fondness for certain chromatin states, and that not all E-boxes are in an environment that can capture MYC. MYC binds with strong preference to E-boxes that are located proximal to CpG islands [252, 254], which are known to define regions of open, active, chromatin [255]. Similarly, MYC binding is also heavily influenced by posttranslational modifications on nucleosomes, avoiding E-boxes buried in heterochromatin but associating with those that carry “active” marks such as histone H3 methylation at lysine residues 4 and 79 (H3-K4/79; [61, 250]). Because these marks are inherited epigenetically and depend on the origin and history of the cell, precisely where MYC is able to bind in any particular cell is likely to be unique. With this in mind, defining a consensus set of MYC target genes is extremely difficult, as every cancer—or even individual cells within a given cancer population—could have different patterns of epigenetic marks that dictate MYC binding.

Third, precisely where MYC interacts with the genome is governed by how much MYC is present in the cell. This is a particularly important issue when comparing normal with tumorigenic states. If targets genes for MYC are rigidly defined according to the criteria stated above, there simply is not enough MYC in a normal cell to bind to all of the targets that have been described. Either MYC has to act in a highly dynamic way, flitting from one gene to another, or we have to redefine targets to parse out those that respond to MYC at physiological versus pathophysiological levels of MYC expression. Careful dosing of MYC has shown that, at low levels, the protein occupies primarily active E-box-containing promoters, but as MYC levels are increased its binding spreads to include enhancers and segments that contain degenerate E-box sequences [61]. Experimentally, the dose-dependent binding of MYC to chromatin means that sites mapped in one study may not necessarily correlate with those in another, where the levels of MYC, or the threshold values that discriminate promoter versus enhancer/variant E-binding, could be very different.

Fourth, MYC can be coerced to new target genes by interaction with other DNA binding transcription factors. Co-binding of transcription factors is emerging as a general theme in eukaryotic transcriptional regulation [256] and recently it was reported that MYC/MAX dimers are recruited by the retinoic acid receptor- α (RAR α ; [257]) to a set of the latter’s target genes (which lack E-boxes). In this way, MYC functions together with RAR α , and in a hormone-dependent manner, to integrate signals that control the balance between

proliferation and differentiation in leukemia cells. If this phenomenon proves to be widespread—and if MYC can be brought to new sites on chromatin by teaming with additional transcription factors—our ability to flag any given gene as a MYC target will depend precisely on the cellular context in which the studies are performed.

Fifth, as mentioned earlier (Section 3.1), MYC is (under experimental conditions at least) a “wimpy” transcription factor, eliciting only modest changes in transcript levels from even its most accepted target genes. The timidity of effects of MYC on transcriptional patterns creates problems teasing bona fide responses out of fundamentally noisy biological data and raises the problem of how to discriminate direct from indirect effects. In the past, inhibition of protein synthesis was often used to ask whether transcriptional changes were a direct or indirect consequence of MYC expression [258], but, as this treatment will also cause rapid clearance of virtually every unstable protein from the cell, the data obtained with this method is unlikely to reflect solely the direct actions of MYC on the transcriptome. The conundrum created by the subtlety of MYC’s transcriptional output is further deepened by the prospect that MYC could enhance transcription globally, either by broad effects on the phosphorylation status of RNA polymerase II [259] or by something as seemingly unrelated as increasing cell size [194], which in turn leads to general increases in transcriptional activity [260].

For the reasons described, therefore, there are as yet no unified and robust criteria for distilling with certainty a set of MYC target genes that underpin its tumorigenic functions. But all is not lost. By analogy to the tumor-relevant properties of MYC discussed earlier (Section 5), the wealth of information on MYC’s transcriptional behavior provides a vital foundation for understanding how MYC can function *in toto*, and elucidation of the individual parameters that determine where MYC acts will—in the context of deeper knowledge of how these parameters are set in a given tumor cell—ultimately lead to an appreciation of how MYC is contributing to tumorigenesis across the spectrum of human malignancies. And it is possible to draw at least one critical consensus point from all of this discussion: MYC binds to and regulates *lots* of genes. This realization is nontrivial because it informs us that searching for ways to target MYC itself is likely to be more efficacious in cancer therapy than seeking the elusive one gene that exerts all of the relevant downstream actions of MYC proteins.

6.2. The “Amplifier” Model. Very recently, two papers emerged [61, 195] that offer a new way of thinking about the actions of MYC on transcriptional processes—the “amplifier” model. In a nutshell, this model states that MYC does not act as a sequence-specific transcriptional activator of specific gene programs but rather works by binding to and amplifying the expression of every gene that is already “on” in a given cell type. In this way, MYC drives tumorigenesis by “amping up” everything a cell does, creating a chaotic state of flux through every biochemical pathway and producing chaos by massive acceleration of cellular processes. This view is very different from past held beliefs that MYC initiates a

discrete set of gene expression changes that push cells on the path to tumorigenesis and provides an intuitive explanation for the wealth of MYC activities that have been described. The model is supported by solid data from a small number of systems, explains how the output of increased MYC burden can be cell and context dependent, and is entirely aligned with previous observations linking MYC binding to preexisting marks of active chromatin [61, 250]. Because it reconciles many of the observations that have confounded past thinking on the genomic actions of MYC, the amplifier model has gained considerable attention in the past year. But it is not without its limitations [261].

One concern with this model is that, at its heart, it is fundamentally very difficult to test. If MYC works by increasing the expression of *everything*, how can we ever hope to resolve whether it is the totality of this transcriptional assault that is important, or whether select genes are particularly important in a given setting? Another concern is that the model is based on data that correlates widespread MYC binding with increases in transcriptional output but fails to show a connection between these processes. In other words, we are still unclear as to whether all of the MYC-bound genes are responding in a direct way to the transcriptional activities of MYC, or whether the more global effects of MYC described above (e.g., increase in cell size) result, indirectly, in the global amplification of transcription. Additionally, because of the recent nature of these reports, we are yet to see whether transcriptional amplification is a general model of MYC action in all cell and tumor types. And finally, the amplifier model fails to account for the actions of MYC in repressing transcription. Indeed, in this model, it is argued that past methods for normalizing transcriptomic data have led to the appearance of a set of MYC-repressed genes [262], but these are in fact nonresponding genes that merely seem to be repressed against the many thousands that are induced. Although concerns over data normalization are certainly valid, this conclusion is hard to reconcile with evidence showing that MYC does repress transcription of select genes and exposing the molecular processes through which this occurs (Section 6.4). It appears, therefore, that while the amplifier model is important and has many appealing characteristics, it needs to be viewed as one of many stepping stones in the evolution of our understanding of MYC. Future efforts to refine the model to include transcription repression and reduce it to a point where clear molecular predictions can be tested in a range of contexts are clearly needed.

6.3. Transcriptional Activation by MYC: A Brief Summary. Many of the important aspects of transcriptional activation by MYC proteins have already been described throughout this review, but a few common points are worth repeating to distill a general view of transcriptional activation, MYC, and cancer. First, MYC binds to and stimulates the expression of many genes—somewhere between many thousand and the entire collection of active loci. Second, genomic targeting by MYC is influenced by many factors, the most important of which appear to be its expression levels and the presence of an E-box within a permissive chromatin environment. Third, MYC stimulates transcription by all three RNA polymerase

FIGURE 8: Mechanisms of transcriptional repression by MYC. (a) *Antiactivation*. In this scenario, MYC represses transcription by blocking the activating functions of another transcription factor; in this case MIZ-1. Association of MYC with MIZ-1 leads to its recruitment to MIZ-1 responsive genes, blocks interaction of MIZ-1 with the p300 histone acetyltransferase, and brings in the DNA methyltransferase Dnmt3a. The effect is to deacetylate histones at the gene (Ac) and cause promoter DNA methylation (Me), thereby shutting down transcription. (b) *Repression by HDAC recruitment*. In this scenario, MYC recruits HDACs to a set of its target genes, directly leading to histone deacetylation and compaction of chromatin structure to inhibit gene activation. Note that the two scenarios may not be independent (i.e., it may be that HDACs are recruited to MIZ-1 target genes in the presence of MYC).

molecules, leading to increases in mRNA, rRNA, tRNA, and miRNA expression. Fourth, MYC achieves gene activation by a number of mechanisms that include promoting the formation of active chromatin via histone acetylation and stimulating the activity of paused polymerase molecules. And finally, MYC activates each of its target genes only modestly. These common themes in transcriptional activation by MYC lead to the very clear impression that MYC takes a “shot-gun” approach towards genome activation—activating lots of genes a little bit—particularly in cancer cells where its levels are unusually high. There are obviously many details to work out and controversies to be resolved, in this area. But the idea that the appearance of high levels of MYC in a burgeoning tumor cell results in widespread but modest activation of gene expression, rather than potent activation of a specific and limited program, is a useful way of reconciling decades of data on MYC function and is a concept that—for now at least—is here to stay.

6.4. Turning MYC Target Genes Off: A Repressed Concept?

The idea that MYC can repress gene transcription has received considerably less attention than its activation potential and as mentioned [262] is now the center of a controversy over whether results from genomic analyses are skewed to overreport the extent with which this activity influences the transcriptome. It must be remembered, however, that the notion that MYC proteins repress transcription is firmly rooted in the MYC field [246] and aligns well with the broader appreciation that many transcriptional regulators function as both activators and repressors (e.g., [263, 264]). While its significance and breadth are under debate, it is worth

reviewing a few of the things we know about MYC-mediated transcriptional repression.

Ironically, the first MYC-repressed gene to be identified was *c-MYC* itself [265, 266], a process that leads to repression of the untranslocated *c-MYC* allele in Burkitt’s lymphoma [267] and one that can be subverted in cancer cells [268]. Since that time, MYC proteins have been shown to repress a host of genes that—not surprisingly—tend to be those with antiproliferative or anticancer properties, such as cell cycle inhibitors [269], tumor-suppressive miRNAs [96], and cell adhesion molecules [270]. But how does this occur? The most prominent mechanism through which MYC can repress transcription is via its association with MIZ-1 [271] (Figure 8(a)). MIZ-1 is a multi-zinc-finger-containing protein that—in the absence of MYC—binds “initiator” elements surrounding the transcription start site of select genes (e.g., the CDK inhibitor p15 [272]) and stimulates their expression, resulting in a potent growth arrest [271]. When complexed with MYC, however, MIZ-1 undergoes a set of changes that include relocalization of MIZ-1 in the nucleus [271], loss of interaction with the transcriptional coactivator and histone acetyltransferase p300 [272], and new association with the DNA methyltransferase Dnmt3a, which methylates the promoters of MIZ-1 target genes [273]. In this way, MYC can be thought to act by reprogramming the transcriptional properties of MIZ-1, preventing recruitment of activating factors (p300) and inducing formation of inhibitory marks (promoter DNA methylation) that conspire to repress MIZ-1 targets. The importance of MIZ-1 to the actions of MYC has been observed in a number of different contexts [246, 270, 272–276] and is perhaps most strikingly demonstrated by

the fact that a single point mutation in MYC that disrupts interaction with MIZ-1 attenuates the oncogenic potential of MYC *in vivo* [275]. Interestingly, the “antiactivation” scheme through which MYC acts on MIZ-1 may ultimately prove to be a common mechanism in MYC-mediated repression, as similar interactions have been reported between MYC and the SP1 [277, 278] and the C/EBP α [279] transactivators.

Additionally, MYC proteins can also directly repress transcription via recruitment of histone deacetylases (HDACs) to chromatin (Figure 8(b)). Targeted recruitment of HDACs by MYC is associated with loss of acetylation of histones [95], a process that leads to nucleosome compaction and establishment of a chromatin environment that is refractory to transcription. As mentioned, MbIII recruits HDAC3 to repress transcription of select MYC target genes [95], and this process is important for repression of tumor-inhibitory miRNAs [96, 280]. MYC proteins also appear to repress transcription by recruitment of HDAC1 [281] and HDAC5 [282], but how and when this occurs is poorly defined at present.

Although large numbers of MYC-repressed genes have been described [283], defining genes that are directly repressed by MYC is as challenging as defining those that are directly activated. And the issue is particularly daunting given the normalization issues mentioned above. What is clear, however, is that MYC associates with proteins that mediate transcriptional repression and that these activities are important in the cases that have been examined. Given the problems noted with simply looking at which genes are turned on and off in response to MYC, we suggest that these repressive interaction partners offer the best entry point for delineating the MYC “repressome.” By tracking how and where MYC associates with the proteins it uses to repress transcription, and correlating these associations with changes in the expression of linked target genes, it will be possible to begin to understand fully which genes are truly repressed by MYC and describe their influence on MYC function.

7. Nontranscriptional Functions of MYC

The issue of whether MYC’s functions depend entirely on its action as a transcriptional regulator, or whether it has activities outside of modulating transcription, is hotly debated. On the one hand, inductive reasoning can be used to make the argument that MYC is a transcriptional regulator, and given its breadth of influence on gene expression there is no barrier from preventing MYC from regulating any biological process via the induction (or repression) of select target genes. On the other hand, MYC does appear to influence some events without the need to act through intermediary gene products, and there is no reason to imagine why it could not be acting through both transcriptional and nontranscriptional mechanisms in both normal and cancerous settings.

Three nontranscriptional actions of MYC have been proposed. The first is based on studies showing that forced expression of the amino-terminus of MYC results in global increases in RNA polymerase II phosphorylation that, in turn, promotes mRNA cap methylation, polysome loading, and mRNA translation [259]. Although the ability of MYC to stimulate RNA polymerase phosphorylation, capping, and

mRNA translation is an inherent function of the wild-type protein [199], the fact that this can occur in the absence of its DNA-binding domain formally establishes the notion that MYC can act outside of sequence-specific DNA binding to influence cellular processes. How this phenomenon contributes to MYC function is presently unclear, but it could feature in cancers where MYC levels are particularly high, and genomic binding sites for the protein are saturated. Perhaps, under these conditions, “excess” MYC is not simply nonfunctional, but rather contributes to gene deregulation by acting globally on RNA polymerase II.

As described in Section 5.4, the ability of MYC to induce replication stress is another process that, in part, is mediated via nontranscriptional mechanisms. Supporting this notion, MYC binds directly to DNA replication factors [284] and associates with origins of DNA replication *in vivo* [284]. Most importantly, however, the effects of MYC on origin activity [284] and DNA replication stress [221] can be reproduced in cell-free settings that are transcriptionally inert, providing compelling biochemical support for the idea that its functions in replication are not dependent on its ability to regulate the expression of genome maintenance genes. At the moment, the mechanisms through which this occurs are opaque, but the development of robust *in vitro* assays for studying MYC in this context should allow the mechanism to be deciphered, selectively inhibited, and their consequences for MYC-driven tumorigenesis understood.

Finally, a recent study [44] showed that calpain-induced cleavage of MYC at lysine 298 (between MbIIIb and MbIV in Figure 2) results in an N-terminal fragment of MYC, “MYC-nick,” that lacks the BR-HLH-LZ and nuclear localization regions of MYC and thus is found in the cytoplasm. This form of MYC recruits the histone acetyltransferase GCN5 to microtubules, where it promotes α -tubulin acetylation, stabilizes microtubule structure, and cooperates with MyoD to induce myogenic differentiation—the opposite of full-length MYC [285]. MYC-nick is widely distributed in tissue culture cell types and abundant in the skeletal muscle and the brain, and its discovery reconciles previously inconvenient findings of MYC in the cytoplasm and its ability to associate with microtubular proteins [286]. It remains to be seen how MYC-nick contributes to—or interferes with—MYC functions in cancer.

Nontranscriptional functions of MYC are understudied and their significance is not well understood. And to many their action may seem foreign and quite disparate from mechanisms of transcriptional regulation. What is particularly interesting, however, is the prospect that nontranscriptional functions of MYC are rooted in the same biochemical activities that allow MYC to regulate gene expression. Stimulation of mRNA cap methylation occurs through TFIIF and P-TEFb—molecules that MYC uses to release paused polymerases and to promote cotranscriptional mRNA capping. Acetylation of α -tubulin by MYC-nick occurs via interaction with GCN5, which is used by MYC to activate transcription through histone acetylation [86]. And although the mechanisms by which MYC influences DNA replicative properties are unknown, stimulation of DNA replication is a common feature of transcriptional regulators that does not depend on

transcription *per se* [287] but rather is linked to the inherent ability of these proteins to promote an open chromatin environment [288]. It is possible, therefore, that nontranscriptional function of MYC will resolve to be as familiar as its transcriptional properties, and that any action that frees MYC of its frank transcriptional functions—such as overwhelming the number of cognate binding sites in the genome or modifying MYC to alter its subcellular localization—can lead to these typically transcriptional biochemical functions being put to new work.

8. Targeting MYC in Cancer

The role that MYC plays in regulating so many pro-tumorigenic functions, together with its extensive—and perhaps absolute—deregulation in human cancer, makes MYC proteins prime targets in the quest to cure cancer. Indeed, it can be argued that broadly effective strategies to treat or cure cancer cannot be realized until therapeutic means to attenuate MYC, or to take advantage of unique properties conferred by MYC on cancer cells, are developed. The topic of targeting MYC in cancer has gained considerable traction in recent years, and a number of excellent reviews have been written on this subject (e.g., [289–292]). Rather than extensively discussing this topic, therefore, we will instead describe some of the key observations that fuel the notion that MYC is a tractable target in cancer and highlight some strategies that are being pursued.

In the past, we typically imagined cancer cells as being akin to an out of control roller coaster, pushed from the apex of normal cell division by a set of collaborating oncogenic events, and propelled downward by accumulated genomic change to metastatic lethal disease. In this way, oncogenes such as MYC act through a “hit and run” mechanism, placing cells in a state where they are irreversibly free to evolve into tumors, but—in well-developed cancers at least—far removed from the initiating events in the cancer cell. Apart from cancer prevention, it is very difficult to see how targeting MYC in this context as a way to treat cancers could work. But fortunately this view is wrong.

In the last decade, the hit and run model for tumorigenesis has largely been replaced by the concept of oncogene addiction—the notion that cancer cells remain physiologically dependent on activated oncogenes for their malignant state [293]. And this is certainly the case for MYC. In numerous mouse model systems, researchers have found that even transient inactivation of MYC leads to tumor collapse [294–297] and even in settings where MYC activation is not the primary driving mutation [298]. Moreover, effective killing of cancer cells in such models does not require complete blockade of MYC activity, but merely attenuating MYC below a certain threshold [299], raising the distinct possibility that moderately-effective MYC inhibitors could have tremendous value in the clinic, and creating a therapeutic window that could kill tumors but leave normal cells unharmed. Although we are yet to see whether spontaneous human tumors are addicted to MYC, the finding that tumor cells continually need MYC inspires hope that strategies designed to target this family could have real clinical value in the future.

In principle, the ways that MYC-driven cancers can be targeted are fairly intuitive: either target MYC itself—at the level of expression or activity—or target some unique property that MYC confers on cancer cells and is required for maintenance of their tumorigenic state. Ideally, these strategies would involve small molecules that can evolve into drugs, they would discriminate between normal and tumorigenic states, and they would exploit a property of MYC that manifests across tumor types, making them as broadly effective as possible. Developing these strategies requires a combination of knowledge of how MYC functions, the weak points in cancer cells, and plain luck.

Theoretically, any of the processes depicted in Figure 4 could be used to interfere with MYC expression in select cancer types. At the level of MYC gene transcription, compounds have been developed that attenuate MYC transcription by inducing unique and inhibitory DNA structures at the MYC promoter [300]. And much excitement has recently been generated over generation of BET bromodomain inhibitors [301–303] that repress MYC transcription by disrupting chromatin-bound events at a distal MYC “superenhancer” [304] and show tremendous promise in a number of pre-clinical models of cancer. At the level of MYC function, a suite of molecules have been developed that target the MYC-MAX interaction (universally acknowledged as being required for MYC activity) [289, 305, 306], although this feat is arguably more difficult than small molecule inhibition of enzymatic function, and important preclinical proof of concept for these molecules is yet to come. Finally, at the other end of the spectrum, the Ub-mediated proteolysis of MYC has gained considerable attention as an attractive target in cancer, spurred by the fact that the Ub-proteasome system relies on enzymatic (i.e., druggable) activities and is already established as a bona fide way to kill cancer cells [307]. Developing molecules that either accelerate the rate of MYC destruction (e.g., by inhibiting deubiquitylating enzymes that stabilize MYC [113, 114]) or massively stabilize MYC to kill cancer stem cells [308] may ultimately prove effective in tumor settings, although these concepts have yet to be reduced to practice.

In parallel with MYC inhibition, a body of literature has emerged exploring the feasibility of targeting the downstream cellular processes that are controlled by MYC and are unique and important for tumor cell maintenance. In the past, considerable effort has been placed on antagonizing the action of specific MYC target genes believed to be central to its function, and, although some successes in this area have been noted [309], the evolution of thinking about MYC targets has led to concerns that this strategy may be too narrow to be broadly effective. Instead, researchers have looked towards common phenotypic characteristics induced by MYC, such as its ability to cause cancer cells to become addicted to glucose and glutamine (Section 5.3), which leads to interest in metabolic therapies (e.g., [310]), or its ability to induce replicative stress, which points to the suitability of replication stress response inhibitors for MYC-overexpressing tumors [311]. The wealth of knowledge of how MYC changes cells provide ample opportunities for targeting MYC in cancer, providing that suitable strategies and effectors can be defined.

Perhaps most exciting in this regard, however, is the possibility that we may no longer have to make educated guesses about which processes are the Achilles Heel of any one cancer type. Development of high throughput RNAi screening technologies now makes it possible to screen the entire genome for genes, that, when knocked down, result in the selective killing of MYC-driven cancer cells. The approach of “synthetic lethality” screening allows for an unbiased survey of gene products uniquely required for survival of cancer cells and is theoretically adoptable to any cancer type that can be grown in culture (and eventually presumably in mouse models of tumorigenesis). The promise of this approach was recently highlighted by the results of a synthetic lethal screen in MYC-driven mammary cell tumors, which were found to be particularly dependent on enzymes in the Ub-related SUMO pathway [312]. The requirement of SUMO for MYC-dependent cancer cell survival was completely unexpected and highlights both the applicability of the method and the extent of what we still have to learn about what MYC does within a cancer cell.

9. Five Simple Rules for Understanding MYC

MYC proteins are complicated. This review has just scratched the surface of a vast wealth of MYC literature and yet presented a complex set of activities, behaviors, and uncertainties in our understanding of MYC. To aid the MYC novice, I have distilled five common “rules” regarding MYC proteins that are not particularly sophisticated but capture much of the lore surrounding MYC and are a useful framework from which to conceptualize MYC and its relationship to malignancy.

Rule no. 1. MYC Is Involved in All Cancers Unless Proven Otherwise. The properties of MYC we have discussed here make it especially beneficial to aspiring cancer cells. Frank changes that alter MYC expression (e.g., amplifications and translocations) occur in many malignancies, but MYC is also silently activated by point mutations and—most commonly—by signaling events that lie downstream of other oncogenic pathways. It is very likely, therefore, that the vast majority of human tumors have lost their ability to control MYC.

Rule no. 2. MYC Does Everything. The litany of effects of forced MYC expression on cells is breathtaking. MYC regulates cellular processes as diverse as growth, metabolism, DNA replication, cell cycle progression, cell adhesion, differentiation, and apoptosis. It can activate virtually every gene. It functions as a transcriptional repressor. And it has actions outside of its canonical transcriptional roles. Whether this impressive repertoire is truly unique to MYC, or simply reflects the intense and sustained scrutiny these proteins have received over 30 years, is debatable. It should also be noted that just because MYC *can* do everything, it is highly unlikely that all of its functions are acting in every cancer cell all of the time.

Rule no. 3. Most MYC Functions Are Exerted via Effects on Gene Expression. Although debate continues as to the

extent to which MYC directly regulates gene expression and the contribution of activation versus repression, the overwhelming body of evidence demonstrates that MYC acts as a transcriptional regulator. Most of the downstream effects of MYC, therefore, can be assumed to result from alterations in the expression of direct and indirect MYC target genes.

Rule no. 4. When it Comes to MYC, Details Matter. It would be useful to be able to distill a sweeping description of MYC behavior that applies irrespective of cell context or experimental conditions, but this is not possible. MYC proteins are finely tuned to the state of the cell. They bind chromatin according to the epigenetic environment in which they exist, exert different effects depending on their levels of expression, and may also behave differently depending on how they have been activated in tumor cells. Experimentally, this means that the outputs we measure depend on the cell type and context, the precise level of MYC proteins in the nucleus, the manner of overexpression, and perhaps factors as innocuous as the presence or absence of epitope tags. It is wise, therefore, to recognize that seemingly incompatible results from different systems may reflect peculiarities of the experimental setup and to seek ways to standardize how we interrogate MYC protein function.

Rule no. 5. MYC Can Be Targeted to Treat and Cure Cancer. Two important facts support this rule: we know that cancer cells remain addicted to MYC, and we know that forced MYC expression alters tumor cells in ways that make them distinct from their normal counterparts (e.g., metabolic reprogramming). Strategies to target either MYC or its downstream effects offer tremendous hope for development of broadly effective cancer therapies and are being led by our wealth of knowledge on MYC and new approaches such as synthetic lethality screening.

10. Future Perspectives

What does the future of MYC research hold? Efforts to develop therapies designed to exploit aspects of MYC biology will surely accelerate and have been flagged by Nobel Laureate James Watson as a top priority in the war on cancer [313]. These efforts will likely involve refining existing molecules and determining their suitability in different cancer types, as well as identifying and validating new targets and developing ways to attack them with drug-like molecules. If nations are intelligent about how they spend their research funds, these efforts will continue to be met with basic research into the MYC proteins themselves, as there is much that remains to learn about MYC. We still do not know how MYC activity is fundamentally different in cancer versus normal cells. Does forcing MYC expression simply lead to a quantitative change in what MYC does, or do new features emerge (this latter scenario seems most likely)? We still do not understand the function of most of MYC protein, particularly regions outside of the TAD and BR-HLH-LZ. We have yet to fully address functional differences between MYC family members that may be relevant to their restricted cancer associations. We do not totally understand how MYC targeted

to its sites on chromatin, particularly its recruitment to noncanonical E-boxes and its specific requirements in terms of nucleosome modifications. We have no clear mechanistic understanding of how MYC stimulates DNA replication and replication stress in the absence of transcription and lack full appreciation of how other nontranscriptional processes feature in cancer. And, perhaps most dauntingly, we have no real perception of how MYC acts in the complex environment of spontaneous human cancers, where a myriad of oncogenic changes are likely to impact how MYC behaves and how it can be reigned in to block tumorigenesis. Another 30 years should sort these things out.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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