MYC — TIMELINE

Reflecting on 25 years with MYC

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Abstract | Just over 25 years ago, *MYC*, the human homologue of a retroviral oncogene, was identified. Since that time, MYC research has been intense and the advances impressive. On reflection, it is astonishing how each incremental insight into MYC regulation and function has also had an impact on numerous biological disciplines, including our understanding of molecular oncogenesis in general. Here we chronicle the major advances in our understanding of MYC biology, and peer into the future of MYC research.

Research on MYC began at a time when the genetic basis of cancer was largely unknown. A quarter of a century has now passed since the human homologue of v-*gag–myc* was discovered (BOX 1). The lessons learned from studying the highly regulated and multifunctional MYC protein have proved instructive to researchers investigating a broad range of fields, including cell biology, cell cycle, apoptosis, development, signal transduction, transcriptional and post-transcriptional regulatory mechanisms, non-coding RNAs, stem cell biology and the molecular basis of cancer (FIG. 1). This Timeline will focus on MYC regulation and function directly pertaining to tumorigenesis. We have made a valiant attempt to highlight the many milestones in this journey, which is fully archived in over 19,000 published articles (TIMELINE).

Mechanisms of MYC deregulation

The oncogenic activation of MYC was initially perplexing. Other oncogenes identified at the time, such as HRAS, were versions of normal cellular genes activated by mutations in the coding sequence. These mutations were conspicuously absent in MYC[1]. Instead, three novel mechanisms of oncogenic activation were identified: insertional mutagenesis, chromosomal translocation and gene amplification (FIG. 2a). A major development within the past decade has been the realization that MYC deregulation is not restricted to gross genetic changes at the *MYC* locus. MYC can be deregulated by any one of several mechanisms that target its expression and/or activity either directly or indirectly (FIG. 2b). These new insights suggest that the impact of MYC deregulation on human cancer incidence is higher than previously thought, and is not restricted to translocations and amplifications of the *MYC* locus.

Insertional mutagenesis. Leukaemogenesis induced by the acutely transforming virus avian myelocytomatosis retrovirus (MC29) is due to retroviral transduction and generation of chimeric *v-gag–myc* (FIG. 2a). However, the neoplastic mechanism of the slowly transforming retroviruses was at first perplexing, and was finally unravelled through studies of avian leukosis virus (ALV). Analysis of DNA and RNA from ALV-induced tumours supported the supposition that viral integration into the host genome could inappropriately activate a nearby cellular oncogene (FIG. 2a). In 1981, B. Neel and colleagues demonstrated the existence of viral–cellular RNA chimaeras and showed that viral integration sites were evident at specific sites in the genome, yielding similar hybrid RNA molecules in independently infected birds[2]. Unlike the acutely transforming tumour viruses, the viral coding regions of their slowly transforming cousins were not involved and were often mutated and/or not transcribed[2,3]. Complementary DNA from five of the viral oncogenes that were known at the time, including *v-myc*, was hybridized to the avian lymphoma RNA, allowing identification of increased levels of *MYC* transcripts fused to proviral sequences in the tumours[4]. MYC was the first cellular oncogene that was shown to be activated through retroviral promoter insertion, and this hallmark observation was independently confirmed within the year[5]. A short time later, murine leukaemia proviral sequences were found adjacent to the *Myc* locus in mice and rats[6]. Taken together, these results implied that the researchers had uncovered a surprising reality: neoplastic transformation could result from the activation of a non-mutated cellular gene. On the basis of this pioneering work with *Myc*, insertional mutagenesis has been widely used as a tool to discover many cellular oncogenes[7] (FIG. 1).

Chromosomal translocation. Molecular analysis of mouse plasmacytomas revealed that the production of *Myc* mRNA resulted from a consistent recombination between the immunoglobin (Ig) heavy chain locus and the *Myc* oncogene[8,9]. Gross chromosomal translocations had been identified in human malignancies, but until human *MYC* was localized to chromosome 8 no direct biological role for these rearrangements had been assigned[10–12]. In Burkitt lymphoma, chromosomes 14, 2 or 22, which harbour the Ig heavy and light chain genes, are translocated with chromosome 8. The *MYC* locus was involved in these translocations, leading to the proposal that the juxtaposition of *MYC* to Ig loci was responsible for the lymphomas (FIG. 2a). In the same year, the oncogenic breakpoint cluster region (*BCR*)–*ABL1* fusion was mapped to the site of chromosomal translocation in the Philadelphia chromosome, but this abnormality generated a novel fusion protein[13]. In the case of *MYC*, overexpression of a non-mutated gene appeared to be adequate for tumour generation. Extensive analysis of the

Box 1 | **The discovery of retroviruses and MYC**

Researchers studying the molecular basis of cancer owe a great debt to P. Rous. In the early part of the 20th century, long before the molecular isolation of genetic material, he demonstrated that an entity causing cellular transformation could be transferred through cell-free filtrates. A retrovirus, now known as the Rous sarcoma virus (RSV), was shown to be the infective agent. The identification of reverse transcriptase in 1970 revealed the replication mechanism of retroviruses, and the purification of this enzyme provided an essential tool for the synthesis of DNA for use in hybridization studies. This enabled the isolation of the transforming sequences within RSV, as these were evident in the DNA of the infected cells. The gene responsible for the transforming potential of RSV was termed *src*. Using information gleaned from the isolation of *src*, the transforming sequence of the MC29 avian tumour virus was identified through hybridization studies and later named *myc*, for myelocytomatosis (the leukaemia caused by this virus). When the same gene sequences were identified in the DNA of non-infected cells, a theory developed: viral oncogenes were commonly captured from the normal cellular DNA. The detection of transforming sequences in tumour retroviruses revolutionized the study of molecular oncogenesis, leading to the identification of countless cellular oncogenes, as reviewed by H. Varmus[269].

Burkitt lymphoma and plasmacytoma translocation breakpoints, as well as the coding region of the activated allele, has advanced our understanding of MYC regulation. This chromosomal translocation was modelled by J. Adams and colleagues in the *Eμ–Myc* mouse, which develops a clonal lymphoma in the B-cell compartment[14]. Activation of human *MYC* as a result of chromosomal translocations is common in haematopoietic tumours[15].

Amplifications. Cancer cells contain many types of karyotypical abnormalities, including homogeneously staining regions and double-minute chromosomes. The manner by which these aberrations can drive cancerous growth was also determined through studying *MYC*. Examination of homogeneously staining regions and double-minutes in colon cancer cell lines and leukaemic HL60 cells revealed that these cells harbour multiple copies of *MYC*[16–18] (FIG. 2a). Amplification of a new Myc member, *MYCN*, (which is normally only expressed during development) was discovered in a panel of human neuroblastoma cell lines and tumour samples[19,20] and was quickly associated with poor patient prognosis[21,22]. With the identification of *MYCL1* (which is also expressed normally only during development), it became clear that a well-documented genetic abnormality evident in lung cancer is the deregulation of one of the three transforming members of the Myc family (MYC, MYCN and MYCL1)[23–25]. More recently, the use of genome-wide scanning strategies revealed that *MYCL1* is amplified in several types of cancer, including ovarian carcinoma[26]. In contrast to chromosomal translocations in haematopoietic cancers, activation of the *Myc* genes by amplification is commonly detected in solid human tumours.

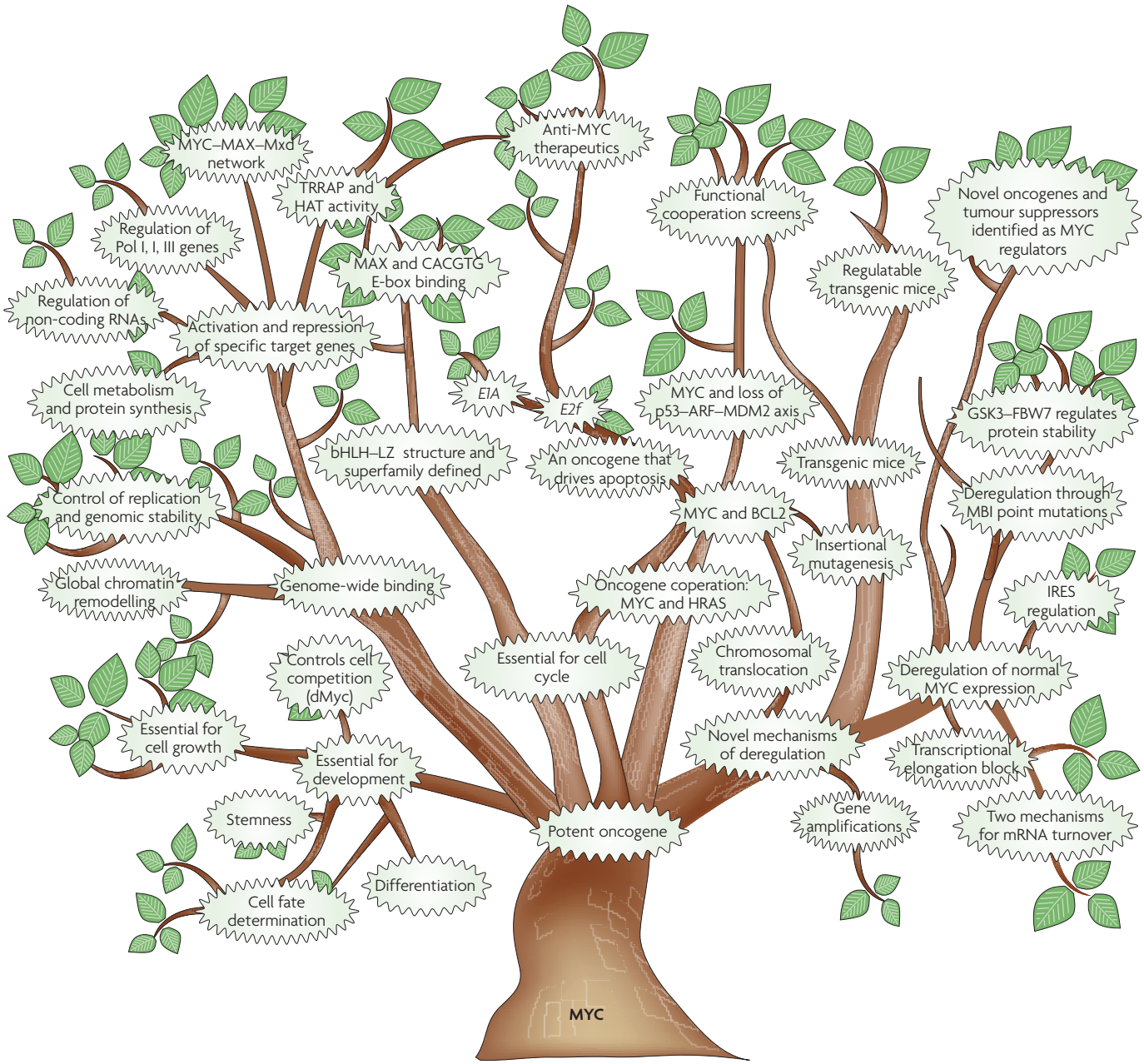
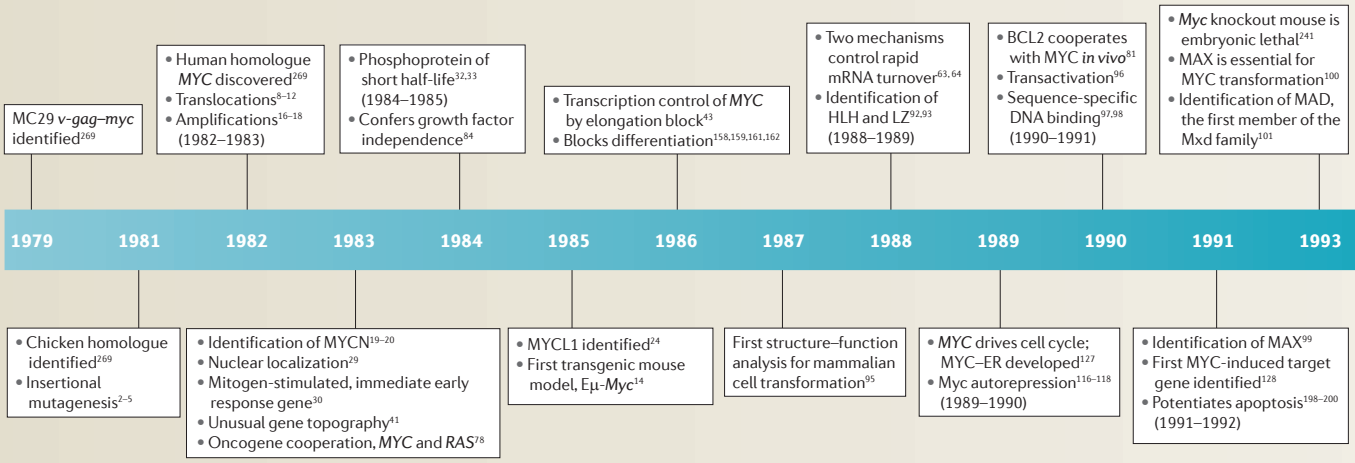


Figure 1 | **The MYC tree of knowledge.** The lessons learned from MYC research branched out and helped to advance many fields.

Timeline | **MYC research and cancer**



APC, adenomatous polyposis coli; HLH, helix–loop–helix; LZ, leucine zipper; TRRAP, transactivation/transformation-associated protein.

The control of MYC expression

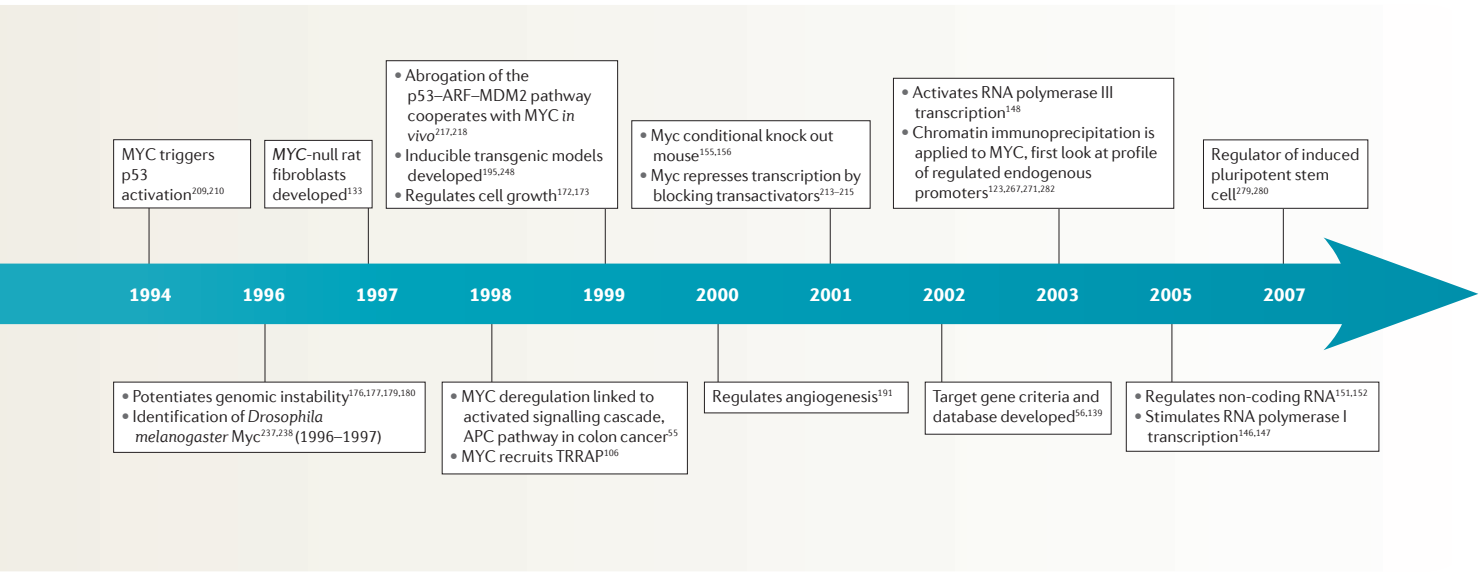
With the realization that the gross genetic abnormalities that activated *MYC* in cancer universally led to deregulated expression of the intact coding region, a series of new questions arose. What is the normal expression pattern of MYC? How is this expression controlled in non-transformed cells?

In the early 1980s, the function of MYC was investigated using antibodies directed against the gag portion of the MC29 v-gag–myc fusion protein. It was shown that v-myc is a nuclear protein that binds to double-stranded DNA[27,28]. S. Hann, while in R. Eisenman's laboratory, demonstrated nuclear localization for the endogenous human protein shortly thereafter[29]. In 1983, Kelly *et al.* established a direct link between mitogenic stimulation of quiescent cultured cells and a rapid induction of *MYC* mRNA. Maximal mRNA levels of this immediate early response gene were reached within 2 hours of mitogen treatment in the presence of cycloheximide, an inhibitor of protein synthesis[30]. The mRNA[31] and protein[32] demonstrated extremely short half-lives, and both were expressed at constant levels once cells were in the cell cycle[33,34]. The phosphorylation pattern of MYC was also described and, like expression, was invariant throughout the cell cycle[33]. Anti-proliferative signals were shown to trigger rapid downregulation in MYC expression[35–38]. Clearly, these data indicated that MYC expression, and presumably MYC activity, was tightly regulated in non-transformed cells and designed to respond quickly to proliferative cues from the extracellular milieu.

Two questions immediately arose: what are the agonists that regulate MYC expression and is the control at the transcriptional or post-transcriptional level? Insight into these issues seemed to be the key to understanding MYC function and so a flurry of research ensued. This period of intense discovery, competition and excitement was peppered with controversy. Many research groups produced convincing, high-quality data that argued for completely distinct mechanisms of regulation. Although these were hotly debated issues at the time, it is now clear that a multitude of signal transduction pathways and numerous regulatory mechanisms have evolved to keep MYC expression under tight control.

Transcriptional control and mRNA turnover. In the mid to late 1980s, MYC transcriptional regulation was a primary focus for many laboratories. The first order of business was to clone and compare *MYC* genomic DNA from a wide variety of species (reviewed in REFS 39,40). The gene was found to have unusual topography, with a large non-coding exon I, followed by coding exons II and III. Several minor TATA-less promoters were mapped as well as the two major, classical TATA-containing promoter start sites at the 5′ end of exon I[41,42]. Two polyadenylation sites were also identified, as were several unusual products of antisense transcription[43–45]. To understand how extracellular stimuli controlled *MYC* transcription, DNAse I hypersensitivity sites were mapped in association with transcription[43,46,47]. Finer mapping was conducted using several assays and distinct response elements and their regulators were slowly defined. However, deciphering the complex regulatory mechanisms of transcription initiation was more of a challenge than for other genes (for discussion, see REFS 39,48,49). In 1986, *MYC* was identified as the first eukaryotic cellular gene to be regulated by transcription elongation control[43,44,50,51], and an elongation block was shown to occur during cellular differentiation. Loss of this control mechanism is evident in cancer. The *MYC* promoter is a key convergence node for multiple signalling cascades that result in an impressive regulatory network (reviewed in REF. 52). The constitutive deregulation of MYC transcription can occur by both direct and indirect effectors, leading to cellular proliferation and transformation[53–59] (FIG. 2b). Study of the regulation of the *MYC* promoter continues to provide new insight into novel transcriptional control mechanisms[52,60].

Research into mRNA turnover was a top priority from the mid 1980s to the early 1990s. Transcription alone could not account for the enormous differential in mRNA expression following either proliferative or anti-proliferative stimuli[38,61]. Rapid *MYC* mRNA turnover was dissected first in *cis* then in *trans* using novel methodologies involving both cell-free systems and intact cells[62]. Two distinct and widely applicable mechanisms of mRNA decay were discovered. The first is a translation-independent mechanism, involving poly(A) tail shortening that is regulated by AU-rich sequences in the 3′ untranslated region[63,64]. The second is a translation-dependent mechanism that is regulated by a region



of mRNA corresponding to the carboxy-terminal domain of the protein, known as the coding region determinant[65]. Increased mRNA expression is evident in tumour cells. However, this was initially controversial: was this a cause or consequence of cellular transformation? Evidence that deregulation of *MYC* mRNA expression was able to drive cancer development was shown with transgenic mouse models[14,66]. The increase in *MYC* mRNA stability in human cancers can result from direct and indirect mechanisms (FIG. 2b).

Protein expression and regulation. The control of MYC expression was analysed in the mid to late 1980s. Although multiple open reading frames have been identified, two encode universally expressed proteins that migrate as p64 and p67 and arise from an AUG codon at the 5′ end of exon II and a CUG initiation codon at the 3′ end of exon I, respectively[40,67–69]. Phosphopeptide analysis revealed that specific serine and threonine residues of MYC were phosphorylated *in vivo* (reviewed in REF. 70). The two residues that have primarily been in centre stage over the last 15 years, Thr58 and Ser62, are important for transformation and regulate both MYC stability and activity[71,72]. On the basis of evidence from several groups, it is thought that proliferative stimuli activate specific kinases to phosphorylate Ser62 and increase MYC stability. Phospho-Ser62 can then serve as a platform for phosphorylation of Thr58 by glycogen synthase kinase 3, enabling the tumour suppressor FBW7 to bind and then recruit the SCF^{FBW7} complex to direct MYC ubiquitylation and proteasomal degradation. Levels of regulation additional to this core model have recently been proposed, suggesting several potential approaches for neoplastic intervention[73–75].

Additional mechanisms to regulate MYC expression have been described within the past decade, and include the discovery of a short form of MYC that arises from translation initiation at residue 100 (REF. 76), and cap-independent translation of *MYC*[77]. MYC stability is an area of much interest at this time and further insight into the role and regulation of the expression of the Myc protein(s) and its activity in transformation is likely to expand further in the coming years.

Oncogene cooperation

It was also through studies with MYC that the concept of oncogene cooperation was established. H. Land, when in the laboratory of R. Weinberg, greatly advanced our understanding of transformation by cellular oncogenes when they attempted to transform primary rat embryo fibroblasts instead of using established, immortal fibroblasts. In these cells, expression of oncogenically activated *EJ-RAS* (an oncogenic variant of *HRAS1*) did not cause transformation as it did in the immortal lines. When *EJ-RAS* was co-transfected with either *v-myc* or *Myc*, however, the cells formed foci *in vitro*. This was the first evidence that cooperativity between cellular oncogenes was required for cellular transformation[78]. These results, in combination with E. Ruley's work establishing that the adenovirus early gene *E1A* could also collaborate with activated T24 *HRAS*, supported the idea that multiple genetic changes might be required for tumours to develop[79]. Building on these findings was the demonstration of collaboration between the anti-apoptotic gene *BCL2* and *MYC* by Vaux in the Adams laboratory[80]. Numerous cooperation studies involving MYC later indicated that an often important function of cooperating mutations is the abrogation of the apoptosis that is induced by oncogenic MYC (see below). Cooperating mutations can decrease the latency of disease or alter the tumour spectrum, as was evident when Strasser *et al.* in the Cory laboratory crossed *Eμ–Myc* with *Eμ–Bcl2* mice[81]. The cooperation model has held true for tumour development in human cell systems as well[82].

How does MYC function?

Despite the enormous progress during the first decade of research in understanding the regulation and oncogenic potential of *MYC*, the function of this nuclear phosphoprotein remained unknown. MYC expression was associated with growth of the cell, and overexpression conferred a reduced dependence on serum for rapid proliferation of tissue culture cells[84]. Two popular models emerged: that MYC was directly regulating DNA replication or that MYC was functioning as a regulator of gene transcription. Support for the former came from an intriguing correlative observation in *Xenopus laevis* showing that maternal MYC was recruited to the nucleus during a period in early development that was transcriptionally silent and characterized by rapid replication[85]. Despite reports that MYC had an important role in replication, excitement was replaced by frustration when these initial results were difficult to reproduce[86]. Interestingly, recent publications have re-awakened serious interest in understanding the role of MYC in DNA

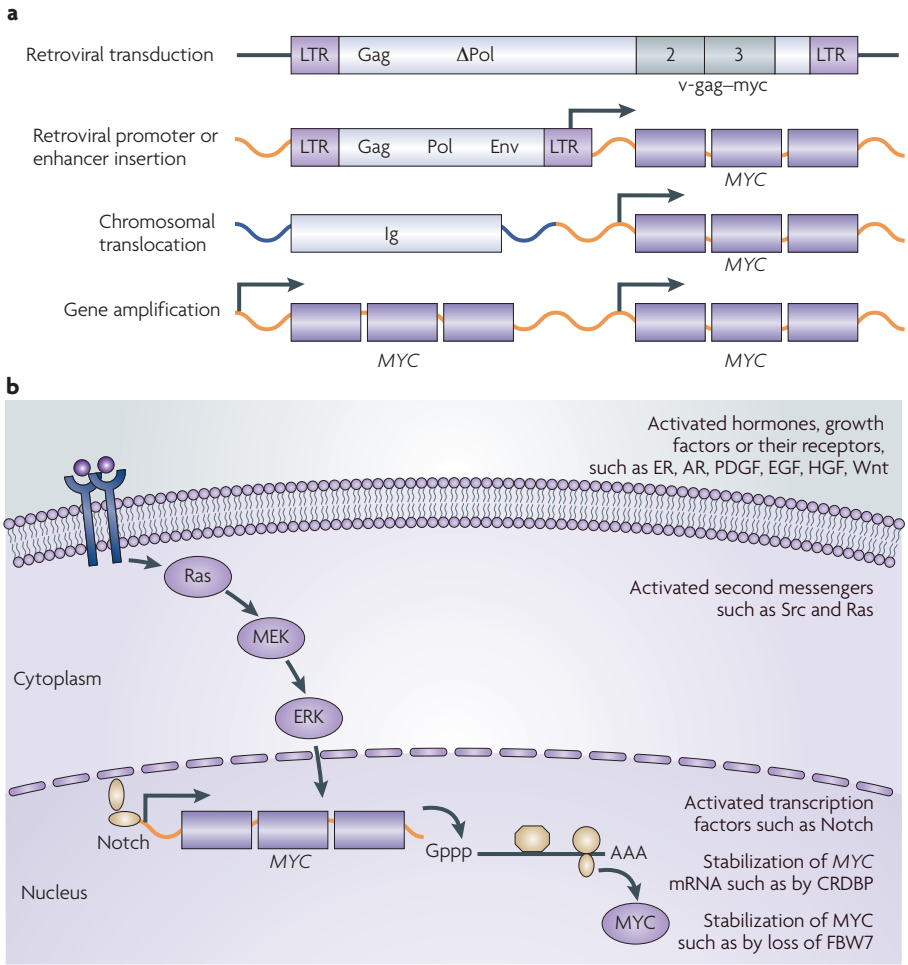


Figure 2 | **MYC deregulation.** Deregulation of MYC expression can occur by many mechanisms. **a** | Originally discovered as a consequence of retroviral transduction, the v-*gag-myc* gene enabled acutely transforming retroviruses to drive tumorigenesis. This led to the discovery that deregulation could also occur as a consequence of gross genetic abnormalities that affect the *MYC* locus, including retroviral promoter or enhancer insertion, chromosomal translocation and gene amplification. **b** | More recently, it has become clear that MYC can be deregulated by many additional mechanisms, including activation of hormones or growth factors, their receptors, second messengers or transcriptional effectors that converge on MYC expression. Alterations in mechanisms that directly or indirectly stabilize *MYC* mRNA and/or protein can also deregulate expression of this potent oncogene.

replication[87–89]. However, in the late 1980s further studies on replication were quickly overshadowed by strong evidence that MYC could function as a regulator of gene transcription (reviewed in REFS 39,90).

MYC as a transcriptional activator. In the mid 1980s it was shown that ectopic MYC expression could modulate promoters linked to indicator genes[91], but it was the characterization of two important domains that revealed the sequence-specific DNA binding and transcriptional activity of MYC. S. McNight's group noticed sequence similarities between several known DNA-binding proteins, including MYC, and through molecular modelling hypothesized the existence of the leucine zipper (LZ) domain[92]. Shortly thereafter, a helix–loop–helix (HLH) domain was identified within MYC[93] (BOX 2). These regions were essential for transformation[94,95]. C. Dang's group then showed direct transcriptional activity of MYC by fusing the amino-terminal domain of MYC, including the MYC homology box II (MBII) region that is crucial for cellular transformation, to the DNA binding domain of the yeast GAL4 protein[96]. Building on these studies, and what had been learned from other basic HLH (bHLH) and bLZ proteins, DNA binding by MYC was observed at last[97,98]. In 1991, E. Blackwood and R. Eisenman provided another crucial missing link. They identified the MYC partner protein MAX and showed that MYC–MAX heterodimers bound a CACGTG E-box sequence with high affinity[99]. Using a series of elegant MYC- and MAX-interdependent binding mutants, B. Amati and colleagues in the Land laboratory showed that MYC–MAX heterodimerization is essential for MYC transformation[100]. Although MYC appears to be dedicated to MAX, MAX binds to members of the Mxd family through the HLH–LZ region[101] and these interactions provide yet another mechanism to functionally regulate MYC activity (recently reviewed in REFS 102–105). The MYC–MAX complex can activate gene transcription by several mechanisms. S. McMahon, while in the laboratory of M. Cole, identified TRRAP (transactivation/transformation-associated protein) as an MBII binding protein that was essential for the transformation activity of MYC[106]. They subsequently demonstrated that, through TRRAP, MYC recruits histone acetylation complexes to chromatin, including the GCN5-containing SAGA complex[107]. Accumulating evidence suggests that MYC also regulates chromatin structure through its interaction with other protein partners including INI1 (also known as hSnf5), which is part of the SWI–SNF ATP-dependent chromatin remodelling complex[108]. This is consistent with a recent study by Knoepfler *et al.* in the Eisenman laboratory showing that loss of MYCN expression results in widespread changes in histone methylation and acetylation, leading to chromatin inactivation, which again is functionally linked to GCN5 (REF. 109). Eberhardy and colleagues in the Farnham laboratory showed that MYC can also increase transcription following the recruitment of RNA polymerase II by promoting elongation through the PTEFb (positive transcription elongation factor) complex[110,111]. New evidence from Cowling and Cole suggests that MYC can also promote RNA polymerase II C-terminal domain phosphorylation and mRNA cap methylation[112]. Clearly the role of MYC as a positive regulator of gene expression is well-established, mechanistically diverse and important for transformation (reviewed in REFS 113–115).

MYC as a transcriptional repressor. One of the first indicators that MYC might also function as a transcriptional repressor came from studies published in the 1980s that suggested that MYC participates in a negative feedback loop. For example, several groups observed that the non-translocated, normal *MYC* allele in Burkitt lymphoma was not expressed. In 1988, it was shown that the product of the *v-myc* gene was able to downregulate endogenous *MYC*[116]. Soon

after, ectopic MYC was shown to suppress transcriptional initiation of endogenous *MYC* in a dose-dependent manner[117]. Structure–function analysis demonstrated that the regions of MYC required for transformation[95] were also required for negative autoregulation[118]. Moreover, loss of autosuppression was associated with more aggressively transformed cells[119]. The idea emerged that MYC repression of target gene transcription might also contribute to transformation. Despite further support for this provocative association[120,121], knowledge of the molecular mechanism of MYC as a repressor lagged behind that of MYC as a transactivator. Insight emerged when the Ziff laboratory showed that MYC could repress promoter activity by a mechanism that was uncoupled from E-box MYC binding sites and dependent upon initiator elements in the basal promoter region[122]. The MBII and the bHLH–LZ regions were also essential for this repression.

Understanding of MYC repression was significantly advanced with the identification of bona fide repressed gene targets and the MYC-binding proteins that are required for repression. The present mechanistic model is that MYC–MAX complexes interact[123] with transcriptional activators that are bound directly to DNA through enhancer or initiator elements, including nuclear factor Y (NFY), SP1 and MYC-interacting zinc finger 1 (MIZ1)[124]. These multi-protein complexes are thought to displace co-activators and recruit co-repressors[125,126]. Genome-wide analyses demonstrate that MYC represses at least as many targets as it activates, further emphasizing the role of repression in MYC function, including transformation.

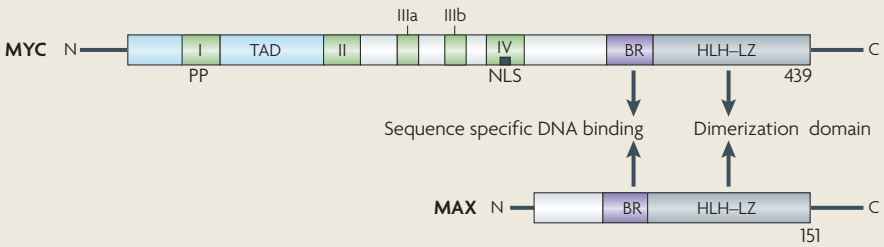
Identifying MYC target genes

One gene at a time. Ten years after the identification of human MYC, its first transcriptional target was identified. A successful strategy developed by M. Eilers while in M. Bishop's laboratory involved the fusion of human *MYC* to the hormone-binding domain of the oestrogen receptor (*ER*), resulting in the conditional, rapidly regulatable MYC–ER fusion protein[127]. MYC–ER activation could drive quiescent cells to enter and progress through the cell cycle[127], and activation of MYC–ER in the presence of cycloheximide identified α-prothymosin (*PTMA*) as a transcriptional target of MYC[128]. Additional MYC target genes, including ornithine decarboxylase 1 (*ODC1*)[129,130], were identified with this approach. Modifications to the hormone-binding domain by Littlewood *et al.* in the Evan laboratory created MYC–ER^{TAM}, which is responsive to 4-hydroxytamoxifen only, allowing *in vivo* use[131]. More than 15 years later, the *MYC–ER^{TAM}* allele is still widely used, and this conditional fusion hormone strategy has been used to regulate a number of other proteins in a wide variety of cell types and mouse models[132].

Another strategy to delineate direct targets exploited the MYC-null rat fibroblast cell system that was developed by J. Sedivy[133] and evaluated whether regulation of expression was dependent on MYC during mitogen-stimulated cell cycle entry[134]. This approach further supported evidence that *GADD45A* and *CAD* were direct targets of MYC repression and activation, respectively[135,136]. Combining both the cycloheximide and MYC-null cell approach certainly distinguished bona fide MYC targets, but this was a slow and labour-intensive screening process[137].

Large-scale analysis. With the new millennium came expression microarrays, providing an opportunity to conduct large-scale analyses of MYC-regulated genes. However, the resulting gene lists showed little overlap between studies. Perhaps one of the greatest challenges that researchers face with MYC is that changes of the mRNA expression levels of MYC-regulated genes are relatively small, exacerbating the poor signal-to-noise ratio that was associated with early expression array analyses[138]. Several criteria for distinguishing true transcriptional targets were delineated[56],

Box 2 | **Regions of human MYC and their roles in transformation**



MYC homology box is a region that is highly conserved between MYC, MYCN and MYCL1, unless otherwise stated[95,113].

Transactivation domain (TAD; amino acids (aa) 1–143)
The TAD can confer activation of gene transcription to a heterologous DNA-binding domain.

MYC homology box I (aa 44–63)
This domain is essential for primary REF co-transformation with activated Ras. Deletion mutants are able to transform Rat-1A cells. Within this region MYC is highly regulated through phosphorylation of Thr58 and Ser62.

MYC homology box II (aa 128–143)
This domain is essential for transformation of REFs and Rat-1A cells, important for transcriptional repression and activation, region of interaction with TRRAP (transactivation/transformation-associated protein) and other cofactors involved in transformation.

MYC homology box IIIa (aa 188–199)
This domain is conserved in MYC and MYCN but not in MYCL1. It is essential for Rat-1A transformation, and shows intermediate transforming potential compared with the activity of the wild type and of an MBII deletion mutant *in vivo*.

MYC homology box IIIb (aa 259–270)
This domain is conserved, but no specific function has yet been assigned to it.

MYC homology box IV (aa 304–324)
This domain is required for focus formation of Rat-1A and RK3E cells. It is dispensable for REF co-transformation focus and Rat-1A soft agar assays.

Primary nuclear localization signal (NLS; aa 320–328)
Subcellular localization to the nucleus is encoded primarily by this region.

Basic region (BR; aa 355–369)
This region is essential for full transformation of primary and immortal cells, and is responsible for specific binding of canonical and non-canonical MYC E-boxes to DNA, with MAX.

Helix–loop–helix–leucine zipper (HLH–LZ; aa 370–439)
This domain is essential for full transformation of primary and immortal cells, and is responsible for interaction with MAX.

Table 1 | **MYC-regulated activities and gene targets associated with transformation**

Functional class	Description of function	Examples of responsible genes*
Cell cycle	MYC–ER activation drives quiescent cells to enter and transit through the cell cycle; primary cells from conditional knockout mice arrest in the absence of MYC expression	Cyclin D2, CDK4 (induced); p21, p15, GADD45 (repressed)
Differentiation	Deregulated MYC blocks differentiation of many cell systems; MYC accelerates epidermal differentiation	CEBP (repressed)
Cell growth, metabolism and protein synthesis	MYC expression levels are associated with body size owing to regulation of cell size and cell number	Lactate dehydrogenase, CAD, ODC, ribosomal proteins, EIF4E, EIF2A (induced)
Cell adhesion and migration	MYC drives tumorigenesis in part by allowing for anchorage-independent growth	N-cadherin, integrins (both repressed)
Angiogenesis	MYC induces angiogenesis in a wide range of tissues	IL1β, miR-17–92 microRNA cluster (induced), thrombospondin (repressed)
ROS, DNA breaks and chromosomal instability	MYC can contribute to instability, trigger telomere aggregation and increase ROS production	MAD2, TOP1, BUBR1, cyclin B1, MT-MCI
Stem cell self-renewal and/or differentiation	Ectopic MYC can potentiate induced pluripotent stem cells; MYC can control the balance between stem cell self-renewal and differentiation	To be determined, potentially genes associated with cell cycle, immortalization, adhesion and migration
Transformation	MYC can drive focus formation and anchorage-indepenent growth *in vitro* and full tumorigenesis *in vivo*; MYC is often deregulated in primary human cancers	Multiple targets are thought to contribute to transformation

This information is adapted from Dang[138]. *For further information see MYC Cancer Gene. CDK, cyclin-dependent kinase; CEBP, CCAAT/enhancer-binding protein; EIF, eukaryotic translation initiation factor; ER, oestrogen receptor; IL1β, interleukin 1β; MT-MCI, MYC target in myeloid cells 1; ROS, reactive oxygen species; TOP1, topoisomerase 1.

and a database (MYC Cancer Gene) was developed by C. Dang to manage and categorize MYC-regulated genes according to these criteria[139].

In recent years, the chromatin immunoprecipitation assay (ChIP) has allowed researchers to better identify true direct targets of MYC. Thanks to this technology we now know that MYC binding to genomic loci is highly dependent on chromatin structure and modification, such as CpG and/or histone methylation[140,141]. Combining the sensitivity and specificity of ChIP with high-throughput array technology (ChIP-chip), or with high-throughput nucleotide sequencing (ChIP-PET and ChIP-seq) further advanced the field[142–145]. For the first time, the entire genetic programme of MYC target genes could be visualized. By integrating these data with the complementary expression array data, MYC-directed pathways can be distinguished.

Experiments performed with these new assays suggest that MYC is a global transcriptional regulator. Unlike other transcription factors, MYC can bind to approximately 10–15% of the genome and can regulate both genes encoding proteins and those encoding non-coding RNA products of several functional classes[138,143]. A common feature among these many arrays is the plethora of genes that regulate the cell cycle and metabolism, including genes that encode ribosomal proteins as well as RNA binding and processing factors, which is consistent with the ability of MYC to regulate transcription mediated by all three RNA polymerases[146–150]. Much excitement has been generated recently about the role of non-coding, regulatory RNAs, and MYC research is at the forefront of these studies as well (FIG. 1). The first oncogenic microRNA polycistron was shown to be regulated by MYC[151,152]. The fields of tumorigenesis, epigenetics and non-coding RNA collided in a report demonstrating allele-specific, oncogenic upregulation of *H19* by MYC[140]. For full coverage of MYC target genes we refer the reader to several in-depth review articles[113,124,153,154].

How does MYC transform cells?

In parallel with the hunt to identify MYC target genes and their mechanisms of regulation, there was an equally voracious appetite to identify and understand the main biological activity and pathway controlled by this potent oncogene. The successful MYC researcher who cracked the case would be heralded for providing a major molecular advance in our understanding of cancer aetiology: the race was on. Little did we know that MYC would be multifunctional and achieve its notoriety as a potent oncogene by regulating many pathways that collectively contribute to neoplasia. A brief overview of the numerous proliferative activities directed by MYC is provided, along with examples of the genes responsible[138], in TABLE 1.

Cell cycle and differentiation. It was clear from the start that MYC had a unique and crucial role in cell proliferation. In cells with activated MYC, G1 is often shortened as cells enter the cell cycle, and MYC is essential for G0/G1 to S phase progression[57,70,155,156]. Work from many groups over the past 15 years has revealed the mechanisms of cell cycle regulation by MYC[56,157]. For example, MYC abrogates the transcription of cell cycle checkpoint genes (for example, *GADD45* and *GADD153*) and inhibits the function of cyclin-dependent kinase (CDK) inhibitors, either through direct repression of gene transcription or indirectly through degradation or sequestration. MYC also promotes cell cycle progression by activation of cyclin D1, cyclin D2, cyclin E1 and cyclin A2, as well as CDK4, cell division cycle 25A (CDC25A), E2F1 and E2F2. This example further reinforces the notion that multiple pathways are regulated by MYC in order to drive any one biological programme.

Although ectopic MYC expression can dramatically block the differentiation of many different cells types, MYC can also stimulate cellular differentiation[158–162]. Several groups have demonstrated that MYC downregulation is required for cells to exit the cell cycle and undergo differentiation. This important point of regulation is further enforced by the induction and function of the Mxd family members in response to differentiation cues[102–105,163–167]. MYC is now well-established as a regulator of differentiation and more recently has been

shown to modulate cell fate. The role of MYC expression during normal development is associated with proliferative expansion and cellular migration. Loss of MYC expression in specific cellular compartments leads to striking phenotypes[168–171]. The relevance to tumorigenesis is intuitive, with deregulated MYC preventing differentiation and promoting migration, leading to the features of aggressive, less differentiated, metastatic cancers.

Cell growth, genomic instability and angiogenesis. In the second half of the 1990s MYC was hailed as having three new talents that promote tumorigenesis: regulating cell size, altering genomic stability and triggering the angiogenic switch. The ability of MYC to promote cell growth (causing cells to double in mass and size) was shown in normal and tumour cells, both *in vitro* and *in vivo* (described below). MYC enables cell growth by providing the cell with an abundant supply of several classes of basic building blocks as well as increasing cell metabolism and protein synthesis[172,173]. When MYC is activated, cellular growth is no longer rate-limiting to the proliferative process. Several MYC target genes are thought to have a role in this activity, including those associated with cellular metabolism, ribosomal and mitochondrial biogenesis, and protein and nucleic acid synthesis. Interestingly, microarray analyses show that these are universal targets, commonly regulated by MYC in a wide variety of cell types[138,174,175].

The second reported skill of MYC was initially described by S. Mai and colleagues, who showed that specific gene amplification occurred at a high frequency in cells with deregulated MYC[176,177]. Additional research shows that MYC can promote chromosomal instability[178–180]. However, because the processes appear to be highly context-dependent, the role of MYC in genomic instability has been a subject of debate and controversy[181–184]. Several mechanisms have been proposed, including increased levels of reactive oxygen species, alterations in chromosome structure[181,185], overcoming the p53 checkpoint[180,186,187], and induction of a DNA damage response and/or replication[89,188–190]. Losing the high-fidelity organization of the genome is a hallmark of tumorigenesis that can clearly be associated with MYC deregulation.

The ability of MYC to promote the angiogenic switch is a non-cell-autonomous activity that was also uncovered in the late 1990s. A. Thomas-Tikhonenko introduced Rat-1A cells *in vivo* as xenografts and showed angiogenesis that was associated with MYC deregulation[191]. Downregulation of thrombospondin is vital to angiogenesis and is potentially achieved through MYC induction of the miR17–92 microRNA cluster[192,193]. S. Pelengaris and G. Evan have shown that, in pancreatic islet cells, increased MYC expression and release of interleukin 1β (IL1β) is crucial for the initiation of angiogenesis[194,195]. More recently, L. Soucek and colleagues have shown that the recruitment and degranulation of mast cells is essential for the subsequent maintenance of angiogenesis during tumour expansion[196,197]. It will be interesting to learn whether new insights into the role of MYC in regulating normal vascular development and inflammation also play a part in tumorigenesis.

Role in apoptosis

The role of MYC in cellular transformation and proliferation was already well-established when a remarkable observation involving MYC was reported in the early 1990s: ectopic expression of the protein sensitized cells to undergo apoptosis[198–200]. In the absence of specific survival factors, deregulated MYC expression invoked a default pathway of cell death[200,201]. Again, observations that were first made while studying MYC were relevant for other oncogenes (FIG. 1), including *E2F1* and *E1A* (reviewed in REF. 202). Researchers now had an explanation for the clonal nature of MYC tumours and the cooperation observed between MYC and BCL2 (REFS 81,203,204). Deregulated MYC alone promoted a hyperproliferative state, which was kept in check by a concomitant increase in cell death. Abrogation of MYC-potentiated apoptosis is crucial for cellular transformation and, once this occurs, clonal tumours can result. The crucial role of MYC in apoptosis has been supported by work in *Myc*-null cells: in the absence of *Myc*, cells are resistant to diverse apoptotic stimuli[205,206]. The precise molecular mechanisms of how MYC induces apoptosis remain unclear; however, once again it appears that multiple pathways are regulated by MYC to potentiate this biological activity (recently reviewed in REFS 202,207,208).

In 1994, the Eick and Hay laboratories provided evidence that MYC deregulation activates the tumour suppressor p53 and triggers apoptosis[209,210]. Zindy and colleagues in the Roussel laboratory showed mechanistically that deregulated MYC upregulates ARF, which in turn activates p53 to regulate a cohort of target genes involved in apoptosis and growth arrest[211]. MYC directs the latter by repressing the expression of the CDK inhibitor p21 through interaction with the transactivator MIZ1 (REFS 212–215). Interestingly, MYC-induced apoptosis is not always dependent upon MIZ1 interaction[212], which demonstrates that multiple pathways are regulated by MYC to potentiate apoptosis. The importance of the ARF–MDM2–p53 pathway in MYC-induced apoptosis is highlighted by the accelerated tumorigenesis evident with the loss of these tumour suppressors in mouse models of MYC oncogenesis[216–222]. The interplay between this pathway and MYC activity continues to be instructive for understanding MYC and cancer. For example, evidence from the Hann laboratory shows that ARF and MYC can partner to selectively control MYC as a transcriptional regulator, leading to apoptosis[186]. Moreover, functional cloning has identified additional oncogenic regulators of the ARF–MDM2–p53 axis, such as BMI1, TWIST1 and CUL7, which can cooperate with MYC in human disease[223–225].

MYC can also sensitize cells to undergo apoptosis by altering the balance of pro- and anti-apoptotic factors, priming the cells for

Box 3 | **MYC messages from the fruit fly**

The diminutive fruit fly is a result of mutation in the gene encoding the *MYC* orthologue, *dm*, and Laura Johnston and Peter Gallant — while in the Edgar and Eisenman laboratories — showed that dMyc controls cell growth at the level of cell size[270]. A. Trumpp, while in M. Bishop's laboratory, showed that decreased *Myc* expression also leads to a small mouse, but the mouse has a reduced number of cells, rather than smaller cells[156]. A potential common mechanism for the ability of MYC to control body size was highlighted by genome-wide analysis of dMyc binding[271]. Like mammalian MYC, dMyc binds to a large number of sites in the genome and controls the transcription of many genes including key regulators of ribosome biogenesis, which are essential for cell growth. Another feature of the dMyc and dMax flies that appears consistent with mammalian MYC is an intact autosuppression mechanism[272]. Moreover, another dMax interactor, dMnt, the orthologue of mammalian MNT, has recently been identified[239,273]. In a recent genetic screen, R. Eisenman's group has identified a novel dMyc-binding protein, the Trithorax group protein Little imaginal discs (Lid), as being functionally involved in dMyc-induced cell growth, and this interaction is intact in mammalian cells[274]. In addition, a recent novel and unexpected discovery from *D. melanogaster* research is the ability of dMyc to regulate cell competition in a dose-dependent manner[275,276].

Table 2 | **Representative mouse models used to study Myc function**

Model	Strategy	Tumours	Refs
Transgenic models			
MMTV–MYC	MYC expression under the control of the hormone-responsive MMTV promoter	Mammary adenocarcinoma developing after first pregnancy	291
WAP–MYC	MYC expression under the control of the mammary-specific, hormone-responsive WAP	Mammary adenocarcinoma, expression in tumour material becomes independent of hormone stimulation	292
Eμ–MYC	MYC expression under the control of the immunoglobulin enhancer	Clonal B-cell lymphoma	14
Myc-null models			
Myc-null	Homologous recombination to eliminate *Myc* expression	Embryonic lethal	241
Conditional *Myc*-null	Uses the Cre–*loxP* system to allow for targeted recombination of *Myc* allele	Used to study the role of *Myc* in tumorigenesis and normal tissue development	155,156
Inducible transgenic models			
tTA Tet-*O*-MYC	Ectopic MYC expression in the absence of tetracycline	Regulatable tumours in T cells, B cells, liver and bone	248
rtTA Tet-*O*-MYC	Ectopic MYC expression in the presence of tetracycline	Regulatable tumours in breast	252,253
MYC–ER^{TAM}	Ectopic MYC activity in the presence of TAM	Regulatable tumours in skin and pancreatic islet cells	194,195,293

ER, oestrogen receptor; MMTV, mouse mammary tumour virus; rtTA, tetracycline-on transactivator; TAM, 4-hydroxytamoxifen; tTA, tetracycline-off transactivator; WAP, whey acidic protein.

death when conditions are appropriate. In the *Eμ–Myc* model of lymphomagenesis, the Cleveland laboratory showed that MYC indirectly suppresses the anti-apoptotic proteins BCL2 and BCL-X_L[226–228]. This is consistent with evidence showing that MYC triggers apoptosis through BAX[229,230] and that MYC protein expression is crucial for the conformational change that activates the pro-apoptotic protein BAX[205,231]. In this way, MYC activity directly influences cytochrome *c* release from the mitochondria, and therefore the activation of downstream effector caspases. Indeed, Eischen *et al.* showed that loss of BAX impairs potentiation of apoptosis by MYC *in vivo*[232]. The Prendergast laboratory showed that MYC sensitizes cells to undergo apoptosis by both p53-dependent and p53-independent mechanisms[233]. The latter is shown by the indirect upregulation of the pro-apoptotic BIM molecule. This was triggered by the observation by the Cory laboratory that *Eμ–Myc*;*Bim*-null or *Eμ–Myc*; *Bim*-haploinsufficient animals quickly developed lymphomas without inactivating the p53 tumour suppressor pathway[234]. Interestingly, the Lowe laboratory engineered mice to express MYC mutants that are evident both in Burkitt lymphoma and in *v-myc* isolates that are known to have reduced apoptotic potential, and these animals succumbed earlier to lymphoma. These mutants were unable to upregulate expression of *Bim* (also known as *Bcl2l11*)[235]. Many elegant experiments clearly show that MYC can sensitize cells to undergo apoptosis and that suppression of this activity is vital to tumorigenesis. By elucidating the pathways through which MYC drives apoptosis, we imagine that the MYC-deregulated tumour could be forced to self-destruct by resurrecting these abrogated pathways, as was recently demonstrated by Goga *et al.* in the Bishop laboratory[202,236].

Insights from model organisms

Use of the fly as a model organism to study MYC function became a serious focus of attention about 10 years ago when *Drosophila melanogaster dMyc* and *dMax* were cloned and shown to bind as a complex to the canonical CACGTG E-box sequence[237,238] (BOX 3). Given that the MYC–MAX–Mxd network has been shown to be conserved in flies, one would predict that this model will continue to surprise and advance our understanding of this multi-talented protein in both invertebrates and vertebrates[154,239,240].

The common house mouse, *Mus musculus*, has been invaluable in revealing the effects of altering MYC expression on both development and disease. In the interest of space, only a limited number of insights can be highlighted (TABLE 2). In 1993, a crucial requirement for MYC was established when *Myc*-null mice failed to develop beyond embryonic day 9.5 (REF. 241). *Mycn* knockout was similarly lethal at embryonic day 10.5, whereas, curiously, *Mycl1*-null mice are viable[163]. In 2001, two independent groups reported the generation of conditional *Myc*-null mice using Cre–*loxP* technology[155,156]. Initial fibroblast and haematopoietic cell studies re-affirmed an absolutely critical role for MYC in the cell cycle. Conditional knockout mice of MYC and MYCN are now being used to identify the precise role of Myc in both tumour and normal tissue, including the recently identified role of Myc in regulating stem cell self-renewal and differentiation[109,168,171,242–247].

Several transgenic animals have been developed to elucidate the mechanism whereby deregulated MYC contributes to tumorigenesis (TABLE 2). In 1999, new mouse models were developed that used two mechanisms to temporally control the expression or activity of MYC. Felsher and Bishop used the Tet-on and Tet-off systems to allow ectopic *Myc* expression to be regulated by the presence and absence of tetracycline, respectively, whereas the MYC–ER^{TAM} system of the Evan laboratory allows ectopic MYC to function in the nucleus only after treatment with 4-hydroxytamoxifen[195,248]. In these experiments, deregulated MYC expression is used to drive tumour growth in specific cell types and then MYC expression is turned off, allowing researchers to observe the consequences of MYC inactivation. In all of the regulatable models tested so far (TABLE 2), inactivation of MYC is sufficient to cause regression of the tumours, through pathways that appear to be specific to the cell type and tumour[249,250]. For instance, in transplanted tetracycline-responsive osteosarcoma tumours, inactivation

of MYC resulted in the regression of tumours and differentiation into mature bone. Following differentiation, reactivation of the MYC allele did not lead to new tumours; instead, the MYC-expressing cells were eliminated through apoptosis[251]. By contrast, inactivation of MYC in mammary epithelial tumours caused initial regression, but neoplastic properties were quickly re-established upon reactivation of MYC. Some tumours even escaped dependence on MYC and returned without reactivation[252,253]. Interestingly, in pancreatic islet cells, researchers were unable to establish tumours upon MYC–ER^{TAM} activation without co-expression of anti-apoptotic BCL-X_L or the loss of tumour suppressors ARF or p53 (REF. 216). Inactivation of MYC again led to regression, and reactivation in this genetic context led to rapid tumour restoration[194]. These studies and others will hopefully determine the conditions under which we might expect cancer patients to benefit from therapeutic targeting of MYC, and those instances in which this approach may not be beneficial or may be optimally used in combination therapy[254,255].

Future directions

This Timeline provides an opportunity not only to reflect on and chronicle the journey of the last 25 years of MYC research, but also to critically evaluate where we are now, be informed by how we got here, and decide the next steps. Where are the immediate gaps and opportunities? Two major areas as well as several additional outstanding and important questions are briefly highlighted. For further insight and discussion, please see the Luscher and Larsson summary of a recent MYC conference[256] and the articles edited by Cole and Henriksson[257].

Exploiting MYC to improve patient care at the level of customized diagnosis and treatment is essential. We now have the technology to develop a diagnostic tool to score oncogenic MYC on the basis of activity as a transcription factor, independently of the multiple mechanisms of MYC deregulation. Certainly, the recent recognition of MYC-associated genetic fingerprints in primary human tumours is an exciting development[258–260], although further testing and validation is required. This line of exploration will also advance fundamental research and address whether MYC controls the self-renewal potential of tumour-initiating cells of certain cell-types (BOX 4). Is it this feature that distinguishes MYC as such an aggressive oncogene? The large fraction of human cancers harbouring deregulated MYC makes it an attractive candidate for targeted therapy. Whereas MYC research was often pioneering in advancing our understanding of gene regulation and function, targeting MYC as an approach in the fight against cancer has lagged behind. Further understanding of MYC structure would strongly support efforts in drug design. A number of anti-MYC therapeutic strategies are currently being investigated, and have been recently reviewed[261–266]. A breakthrough in the development of an effective MYC therapeutic could mark a key advance in cancer treatment.

MYC is often described as functioning in a context-dependent manner, yet this remains ill-defined at a molecular level. MYC is downstream of many signal transduction pathways, functioning as a central hub that integrates multiple intracellular and extracellular cues. MYC then processes and interprets these instructions, much like the central processing unit of a computer. Such a network manager is essential in higher organisms, which might explain why MYC is not evident in worms and yeast. We envision this central processing unit function at a molecular level as the regulation of post-translational modifications, which then alter MYC activity through any number of changes, including expression, stability, cofactor binding and DNA occupancy. MYC may bind to many sites in the genome to remain nimble and orchestrate the genetic programme that is dictated by signalling. The number of MYC molecules per cell is also influential, as MYC function is often dose-dependent. Evidence from B. Amati's group suggests that DNA binding site occupancy is based on relative affinity, histone marks and chromatin configuration[141,267]. Clearly, all signalling is significantly determined by the type and transformation state of the cell[53,150,268]. Understanding signal integration and outcome, as it relates to MYC regulation and function, remains a challenge that needs attention. Embedded in this task is the incorporation of the many feedback and feed-forward pathways in which MYC participates.

Answers to several additional discrete questions regarding the mechanism of MYC action remain a focus of future research endeavours (BOX 5).

This journey of discovery has shown that MYC is like no other oncoprotein — always full of surprises and rarely conforming to the expected models. Clearly with MYC research it is important to think outside the box, design well-controlled experiments, and let the data guide the interpretation of results and the design of next steps. Stay observant and do not shy away from bizarre, unexpected results; they are probably real.

Summary

A friend and colleague, J. Woodgett, recently jested that MYC researchers would probably never be unemployed. MYC has been, and still is, a challenging yet fascinating study. Many new insights into the regulation and function of MYC have pushed the boundaries of our understanding of the fundamental mechanisms of normal and neoplastic cell growth, death and development. The next phase of MYC research promises to be as challenging and rewarding as the first 25 years.

Box 4 | Stemness and self-renewal potential

The newest addition to MYC's already illustrious list of abilities is regulation of cell 'stemness'[277]. Through conditional knockout mouse analysis, the Trumpp and Eisenman laboratories have shown that *MYC* and *MYCN* were essential in the normal developmental control of haematopoietic and neuronal stem cells, respectively[168,171]. Mouse embryonic stem cells are dependent on leukaemia inhibitory factor (LIF) for maintenance and the Dalton laboratory showed that MYC is essential and can functionally substitute for this activated signalling pathway[278]. In 2007, MYC was one of four genes in a cocktail that was shown to re-programme pluripotency in a normal terminally differentiated primary fibroblasts to generate an induced pluripotent stem cell (iPS)[279,280]. Thankfully for the purposes of regenerative medicine, MYC is dispensable for iPS development[281]. However, the implications of this novel stemness function of MYC in the context of controlling the putative tumour stem cell cannot be ignored[277]. Evidence from several mouse models, including the Felsher model of MYC transformation of hepatocellular cancer[283], supports the notion that MYC deregulation has an important role in the initiation and maintenance of the tumour stem cell. It is intriguing that the tumour stem cell signature is evident in tumours that are undifferentiated and aggressive — molecular and phenotypical features that are reminiscent of MYC-activated tumours[83,144,260,284–286]. Further links between stemness and MYC emerge with every update of PubMed. For example, S. McMahon recently showed that a novel member of the stem cell signature, USP22, is a co-activator that is essential for MYC transformation[287]. Clearly this field is in its infancy, but it promises to determine whether the frequently poor prognosis of MYC-activated tumours is due to MYC enabling the expansion and maintenance of the tumour-initiating cell.

Box 5 | **Key unanswered questions**

- Are there transformation-associated mutations in MYC that have not yet been identified? With high-throughput sequencing of whole genomes of normal and tumour cells, this interesting question will soon be answered. Similarly, do MYC-associated single nucleotide polymorphisms have a role in cancer development and, if so, how?
- Does MYC binding to chromatin serve transcription-independent functions, including the regulation of chromosomal integrity, gene expression, chromatin structure, cellular replication and genomic instability? Prompted by several recent reports, these lines of investigation require further attention.
- To learn how MYC is able to distinguish itself as such a universal and aggressive oncogene, a vital next step is to functionally discriminate the genes, pathways and biological activities that MYC controls to drive transformation. To distinguish which are functionally crucial, approaches that are likely to be fruitful include high-throughput or gene-specific small interfering RNA screens.
- As a regulator of gene transcription, how is it determined when MYC will function as a transcriptional activator or repressor? How are the many mechanisms of MYC regulation of gene expression integrated or coordinated at any given target? Which targets are regulated by MYC alone and which are dependent on MYC in conjunction with a cooperating transcription factors?
- Are there MAX-independent functions of MYC? Are there functions for MYC outside of the nucleus?
- How does MYC direct cell competition and is this important in cancer?
- How is MYC regulated in the stem cell and how does MYC regulate stem cell fate?
- Given the incredible selective pressure to block MYC-potentiated apoptosis in the tumorigenic process, it seems logical that many more mutations exist to affect this important cooperating event. These will probably be cloned using functional cloning strategies. Similarly are there cooperating mutations that overcome the MYC-induced DNA damage response?
- MYCN and MYC are interchangeable for development[288], but are they functionally equivalent in transformation? Why is MYCL1 so different?
- Given that so many viruses harness MYC to promote their own life cycle (for examples see REFS 289,290), it is likely that the cancer cell has devised similar mechanisms to exploit and deregulate MYC protein for further expansion. Viruses have always been a rich resource for understanding oncogenesis. What additional lessons can be learned?
- Is MYC stability altered at specific subcellular locales, or when in partnership with certain DNA, RNA or protein molecules, or as a mechanism to regulate function, or in response to becoming decorated with one or more post-translational modifications?

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DATABASES

Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
ABL1 | *BCL2* | *Bcl2l11* | *BCR* | *GADD45A* | *H19* | *HRAS1* | *MYC* | *MYCL1* | *MYCN* | *ODC1* | *PTMA*
National Cancer Institute Drug Dictionary:
http://www.cancer.gov/drugdictionary/4-hydroxytamoxifen
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Burkitt lymphoma
UniProtKB: http://www.uniprot.org
ARF | BAX | BCL-X$_L$ | BMI1 | CDC25A | CDK4 | CUL7 | cyclin A2 | cyclin D1 | cyclin D2 | cyclin E1 | E2F1 | E2F2 | FBW7 | HRAS | INI1 | LIF | MAX | MDM2 | MIZ1 | MNT | MYC | p21 | p53 | SP1 | TRRAP | TWIST1 | USP22

FURTHER INFORMATION

Linda Z. Penn's homepage: http://www.pennlab.ca
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