Biochimica et Biophysica Acta 1846 (2014) 457–467

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

MYC deregulation in lymphoid tumors: molecular mechanisms, clinical consequences and therapeutic implications

Tomasz Sewastianik [a], Monika Prochorec-Sobieszek [a], Bjoern Chapuy [b], Przemysław Juszczyński [a,*]

[a] Institute of Hematology and Transfusion Medicine, Department of Diagnostic Hematology, Indiry Gandhi Str. 14, 02–776 Warsaw, Poland
[b] Dana-Farber Cancer Institute, Harvard Medical School, Department of Medical Oncology, 450 Brookline Avenue, Boston, MA 02215, USA

ARTICLE INFO

Article history:
Received 24 March 2014
Received in revised form 28 August 2014
Accepted 28 August 2014
Available online 6 September 2014

Keywords:
MYC
Burkitt lymphoma
Diffuse large B-cell lymphoma
Double hit lymphoma
Targeted therapy

ABSTRACT

MYC is one of the most frequently deregulated oncogenes in human malignancies. It encodes a leucine zipper transcription factor that modulates a broad spectrum of cellular genes responsible for enhancing cell proliferation, cellular metabolism, growth, angiogenesis, metastasis, genomic instability, stem cell self-renewal and reduced differentiation. MYC functions predominantly as an amplifier of expression of already active genes, potentiating the pre-existing transcriptional program, although it can also repress certain transcriptional targets. In mouse models, MYC induces lymphomas, but requires cooperation with other lesions, including inactivation of the p53 pathway, structural alterations of BCL2 family members, or increased PI3K activity. In human B-cell tumors, *MYC* rearrangements involving the 8q24 region and immunoglobulin heavy or light genes are a hallmark of Burkitt lymphoma (BL), but can also occur in other lymphoid malignancies, that include diffuse large B-cell lymphoma (DLBCL), B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU), plasma cell myeloma (PCM), mantle cell lymphoma (MCL) and plasmablastic lymphoma. For non-BL lymphoid malignancies, *MYC* fusions represent secondary genetic events and exist in the context of complex karyotypes. Regardless of the mechanism deregulating *MYC*, lymphomas over-expressing MYC are addicted to this oncogene, highlighting the potential clinical utility of MYC targeting strategies. Several promising approaches for pharmaceutical intervention have been suggested which are now in preclinical or clinical development. Herein, we therefore review the molecular pathogenetic mechanisms associated with *MYC* deregulation in human B-cell lymphomas and their implications for therapies targeting MYC.

Contents

1. Introduction

MYC (v-myc myelocytomatosis viral oncogene homolog) is one of the most frequently deregulated oncogenes in human malignancies. It belongs to a family of oncogenic proteins, first described in the avian myelocytomatosis retrovirus MC29 causing spontaneous

* Corresponding author. Tel.: +48 22 34 96 305; fax: +48 22 34 96 237.
E-mail address: pjuszczynski@ihit.waw.pl (P. Juszczyński).

http://dx.doi.org/10.1016/j.bbcan.2014.08.006
0304-419X/

myelocytomatosis in chickens [1,2]. The human homologue of the avian oncogene was identified in translocations involving the 8q24 region and immunoglobulin (*IG*) heavy and light chain genes at chromosomes 14, 2 and 22 in Burkitt lymphoma (BL) [3,4]. The translocation juxtaposes the *MYC* proto-oncogene to immunoglobulin locus regulatory elements, resulting in the uncontrolled expression of *MYC*. Although deregulation of MYC is a defining feature of BL, it is not specific to this entity and occurs also in diffuse large B-cell lymphoma (DLBCL) and other B-cell malignancies. Oncogenic properties of over-expressed MYC were confirmed in a transgenic mouse model, where *Myc* gene was expressed under the control of immunoglobulin enhancers (Eμ-*Myc*). Mice developed clonal pre-B and B-cell lymphomas with a latency of 4–6 months [5]. Expression of *Myc* under the control of *IG*λ light chain enhancer, preserving all the elements required for establishment of a locus control *in vivo*, resulted in tumors even closer resembling human BL [6].

In mouse models Myc is essential for development of hematopoietic system where it fine-tunes the balance between self-renewal and differentiation of hematopoietic stem cells [7–9]. During different stages of lymphocyte development, Myc expression varies and in general reaches highest levels in proliferating cells [10]. In mature B lymphocytes, Myc expression is induced by antigen encounter and T cell contact, and is subsequently repressed by Bcl6 upon germinal center (GC) formation. Rapidly proliferating centroblasts in GC dark zone (DZ) lack Myc expression, contrary to a subset of light zone (LZ) centrocytes. Positively selected centrocytes express Myc, reenter cell cycle and are designated for DZ remigration or differentiation into plasmablasts. In B-cells undergoing plasmacytic differentiation, Myc expression is repressed by Blimp-1. This biphasic kinetics of Myc expression in GC cells is essential for GC reaction in mice, as MYC ablation *in vivo* leads to lack of GCs [11–13]. The expression of MYC in a subset of GC B-cells is particularly important for human B cell lymphomagenesis, since these tumors originate mostly from GC B cells and frequently involve *MYC* chromosomal translocations. Of note, GC-B cells express the activation induced deaminase (AID), required for the formation of DSBs in the mouse *Myc* locus, since in the absence of AID, *Myc*/*IgH* translocations do not occur [14,15]. Since the Myc + GC B cell subsets also exist in humans, they may represent a stage of GC B cell differentiation prone to malignant transformation due to MYC breakpoints [11].

1.1. Deregulation of MYC in human lymphomas

Expression of MYC is a defining feature of BL, which is a highly aggressive B-cell tumor manifesting as a rapidly enlarging mass with predilection to extranodal involvement. Three subtypes of BL are distinguished in the current WHO classification: endemic, sporadic and immunodeficiency-associated [16,17]. BL exhibit a very high mitotic index as measured by Ki67 staining which is present in up to 100% cells [18]. *MYC* (8q24) translocates to the immunoglobulin heavy (*IGH*) gene locus (14q34) in about 85% of cases and less frequently to light chains κ (2p12) and λ (22q11) gene loci [19] (Table 1). In the endemic subtype translocations are caused by somatic hypermutation (SHM) or occur during aberrant *VDJ* (variable, diverse, and joining gene segments) recombination and are located 5' to the joining regions [20,21]. In sporadic and immunodeficiency-related BL, the *MYC* gene is usually joined to *IGH* switch regions, suggesting that the translocations occur due to aberrant resolution of double strand breaks (DSB) caused by an AID-initiated class switch recombination (CSR).

Rare BL cases lack *MYC* translocations, but exhibit the typical phenotypic features of BL. Regardless of the presence of *MYC* translocations, its expression in all BL cases is similarly up-regulated [22,23]. In these cases, MYC expression is likely driven by other mechanisms, including microRNAs. For example, the expression of MYC-targeting let-7c is lower in all BL cases. Similarly, the expression of other MYC-targeting microRNAs, miR-34b and miR-9, are decreased only in BL cases without *MYC* translocation, suggesting that these mechanisms at least partially contribute to MYC over-expression in BLs lacking translocations of this oncogene [23,24]. Rare BL cases lacking *MYC*-breakpoint share a peculiar pattern of chromosome 11q aberrations, characterized by interstitial gains including 11q23.2-q23.3 and telomeric losses of 11q24.1-qter. The 11q abnormalities are recurrently associated with morphologic and

Table 1
Deregulation of MYC in lymphoid malignances.

Lymphoma/Leukemia	Frequency of MYC rearrangements and background cytogenetic features	MYC fusion partners	References
Burkitt lymphoma	>90% of cases; primary genetic event Simple karyotype	*IGH-MYC*; t(8;14) – 85%, *IGκ*, *IGλ-MYC*; t(2;8), t(8;22) – 15% of translocated BLs	[19,30,38]
Diffuse large B-cell lymphoma	7–14% of *de novo* cases, usually a secondary genetic event *BCL2* and/or *BCL6* rearrangement ("double hit" or "triple hit" lymphomas); Complex karyotype	*IG-MYC*-70% *non-IG* (*BCL6*, *BCL11A*, *PAX5*, *IKAROS*)-*MYC* – 30%	[40–42,150,151]
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL	35–50% of cases *BCL2* and/or *BCL6* rearrangement ("double hit" or "triple hit" lymphomas); Complex karyotype	non-*IG*, *IGκ*, *IGλ-MYC*, rarely *IGH-MYC*;	[30,38]
Plasmablastic lymphoma	50% of cases Without *BCL2* and/or *BCL6* rearrangement Complex karyotype	*IG-MYC*, usually *IGH*	[46]
Plasma cell myeloma	15–50% of cases Secondary genetic event Complex karyotype	*IGH*, *IGL-MYC* and non-*IG-MYC*	[152,153]
Acute lymphoblastic leukemia/lymphoma	5% of adult ALL: t(8;14), t(8;22) t(2;8) and 2–5% of children ALL	*IGH*, *IGL-MYC*	[154]
Transformed follicular lymphoma	~8% of transformed FL to DLBCL ~50% of "double hit" lymphoma represent transformation of FL Secondary genetic event Usually complex karyotype	*IGH-MYC*; t(8;14), *IGL-MYC*; t(8;22) or non-*IG* partner genes	[155–157]
Mantle cell lymphoma	26 described cases Secondary genetic event Complex karyotype	*IGH*, *IGL-MYC* and non-*IG-MYC*	[158]
Chronic lymphocytic leukemia	>1% of cases Secondary genetic event del(17p)/monosomy 17, del(11q), and/or complex karyotype	Usually *IGH-MYC*, *rarely IGκ*, *IGλ-MYC*, *non-IG-MYC*	[159]

clinical features of BL in MYC-negative high-grade B-cell lymphomas. The mechanisms underlying the clinical and phenotypic similarities of these tumors to *MYC*-breakpoint positive BLs are currently largely unknown [25].

While *MYC* rearrangements and over-expression are diagnostic features of BL, they are not specific for the disease and also occur in other B-cell tumors (Table 1). In DLBCL, the most common non-Hodgkin lymphoma in adults, *MYC*, after *BCL6* (B-cell CLL/lymphoma 6) and *BCL2* (B-cell CLL/lymphoma 2), is the third most commonly translocated oncogene found in about 7–14% of cases [26,27]. *MYC* rearrangements in DLBCLs are often secondary genetic events related to disease transformation. *MYC* translocations are the predominant mechanism causing over-expression of this oncogene, although gene amplifications and aberrant SHM targeting the 5′ end of *MYC* coding sequence play a role in a fraction of cases [28,29]. In contrast to BL, *MYC* translocations in DLBCL involve more frequently the light chain or non-*IG* partners and occur within a background of complex karyotypes [30]. The most common cytogenetic abnormality accompanying structural abnormalities of *MYC* is the translocation t(14;18) involving *BCL2*. *MYC* translocations concurrent with *BCL6* rearrangements are less frequent. B-cell tumors harboring *BCL2* and/or *BCL6* translocations concurrent with *MYC* lesions, (i.e. "double hit" or "triple hit" lymphomas), frequently exhibit atypical morphologic and/or immunophenotypic features as well as particularly aggressive clinical behavior with rapidly enlarging mass and advanced stage including involvement of extranodal sites, the bone marrow and the central nervous system (CNS) [31,32]. Double-hit cases are usually refractory to multi-agent chemotherapy and patient survival time is very short, in the order of months [31,32]. Consistent with the more complex phenotype and genetic background of non-BL tumors with *MYC* rearrangement, (when compared to BL), these tumors also exhibit distinctive gene expression profiles [30,33]. In addition, in a fraction of *MYC* breakpoint-positive cases that lacked the molecular BL signature, a non-*IG* partner was involved in the *MYC* breakpoint, suggesting that the non-*IG* gene locus exhibits different regulatory properties than *IG* loci. The double MYC/BCL2-translocated DLBCL cases are relatively rare (only ~3%), but the overexpression of MYC and BCL2 protein is a much more frequent feature in these tumors (approximately one third). DLBCLs with overexpression of these proteins are characterized by an aggressive clinical course and demonstrate high-risk gene expression signatures. The immunohistochemical detection of MYC expression can be therefore used to identify the biologically and clinically distinct cases of MYC-driven DLBCLs characterized by an inferior outcome [34–36].

MYC rearrangements are also a typical feature of a rare diagnostic entity termed BCLU (B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma), occurring in approximately 35% to 50% of cases [37–39]. Morphologically, BCLUs are heterogeneous and do not exhibit a coherent set of diagnostic features typical to either BL or DLBCLs. Unlike in BL, *MYC* rearrangement in BCLUs usually do not involve the *IGH* gene, instead *IGκ* and *IGλ* or non-*IG* genes are rearranged [39]. In a subset of BCLU, *MYC* translocations coexist with *BCL2* breakpoints (double hit lymphomas).

Regardless of the involved translocation partner, genetic abnormalities of *MYC* rearrangements in lymphomas are associated with a more aggressive phenotype of tumor cells and an inferior prognosis, largely independent of other clinical and molecular risk factors [40–42]. When treated with R-CHOP (rituximab–cyclophosphamide, doxorubicin, vincristine, and prednisone), patients with *MYC*-rearranged DLBCLs have a shorter progression-free survival (PFS) and overall survival (OS), compared to those having tumors without the translocation [35,43,44]. Furthermore, *MYC*-rearranged tumors exhibit significantly more frequent CNS involvement at relapse [41]. *MYC* is also deregulated in other lymphoid tumors, including acute lymphoblastic leukemia (ALL), multiple myeloma (MM), mantle cell lymphoma (MCL) and follicular lymphoma (FL) [45–47], (Table 1). Irrespective of the tumor type, enhanced MYC expression is a poor prognosis marker [38,40,41].

2. Biological basis of MYC function

2.1. Control of MYC turnover

MYC encodes a basic helix-loop-helix leucine zipper transcription factor located predominantly in the nucleus [48]. In resting cells both MYC mRNA and protein undergo rapid turnover [49,50]. Upon mitogen stimulation, the MAP-ERK (mitogen-activated protein kinase 1) kinase pathway stabilizes MYC protein by phosphorylating serine 62 (Ser62), (Fig. 1A). A similar MYC protein stabilization is caused by the activation of the AKT (v-akt murine thymoma viral oncogene homolog) pathway with the ensuing inhibition of GSK3 or inhibition of PP2A phosphatase [51,52]. MYC is also a substrate for other kinases, such as PIM1 and PIM2 (proto-oncogene serine/threonine-protein kinase) which stabilize the MYC protein by phosphorylating Ser329 and altering the phosphorylation status of Thr58 and Ser62 [53] (Fig. 1A).

2.2. MYC binding partners

Biological activity of MYC largely depends on the binding partners that either mediate transcriptional activation or repression. For activation, MYC forms a heterodimer with MYC associated factor X (MAX) [48]. MYC-MAX heterodimer binds to the E-box consensus sequence (CACATG) and serves as a platform for other proteins involved in chromatin remodeling and transcriptional regulation (Fig. 1B), [48,54–59]. MYC represses genes when it is not bound directly to DNA, but instead is recruited by the MIZ1 transcription factor [60]. MYC hinders the attachment of positive cofactors to MIZ1 and recruits DNA methyltransferase 3A (DNMT3A) and histone deacetylase 3 (HDAC3) which alter chromatin configuration making it less accessible [61]. Another mechanism of repression is through competitive inhibition of MYC by MAX binding protein (MNT) and MAX dimerization protein 1 (MAD) which can also dimerize with MAX and thus exclude it from complexes with MYC [62,63]. MAD/MNT-MAX dimers bind to the E-box sequence and indirectly recruit histone deacetylases in the proximity of regulated gene promoters causing repression of gene transcription [64].

3. Biological consequences of MYC activity

Although MYC modulates expression of genes involved in multiple aspects of cell biology, no single subset of MYC "target genes", accounting for its oncogenic activity has been identified and MYC "target gene sets" from different tumor types show only a partial overlap [65–72]. These unique characteristics of MYC can be explained by studies demonstrating that, unlike "conventional" transcription factors (which bind their consensus sequences and establish their own new transcriptional programs), MYC binds to promoters of already active genes, but has little effect on silent genes. In contrast to these "conventional" sequence-specific transcription factors which exhibit bi- or multimodal distribution of DNA binding (site–specific promoter binding against a background of nonspecific binding to the rest of the genome), MYC distribution is unimodal [73]. In both normal mouse B cells and human tumor cell lines, MYC localizes to "open" chromatin and RNA polymerase II (Pol II) on the promoters of transcribed genes [73,74]. At these core promoters, MYC colocalizes also with CDK9, the catalytic subunit of P-TEFb (positive transcription elongation factor b). After P-TEFb is recruited by MYC, CDK9 phosphorylates Pol II at Ser2, augmenting the elongation of mRNA and facilitating the release of Pol II paused at the promoters of transcribed genes [75]. Of note, in cells inducibly overexpressing MYC, phosphorylation level of Pol II Ser5, associated with increased initiation of transcription, remains unchanged. As a consequence, over-expression of MYC significantly elevates the cellular RNA content by increasing the transcription of already active genes. In cells expressing low levels of this transcription factor, MYC binds to canonical, high-affinity E-boxes in the core promoters of actively transcribed genes, however, with increasing expression of MYC, non-canonical

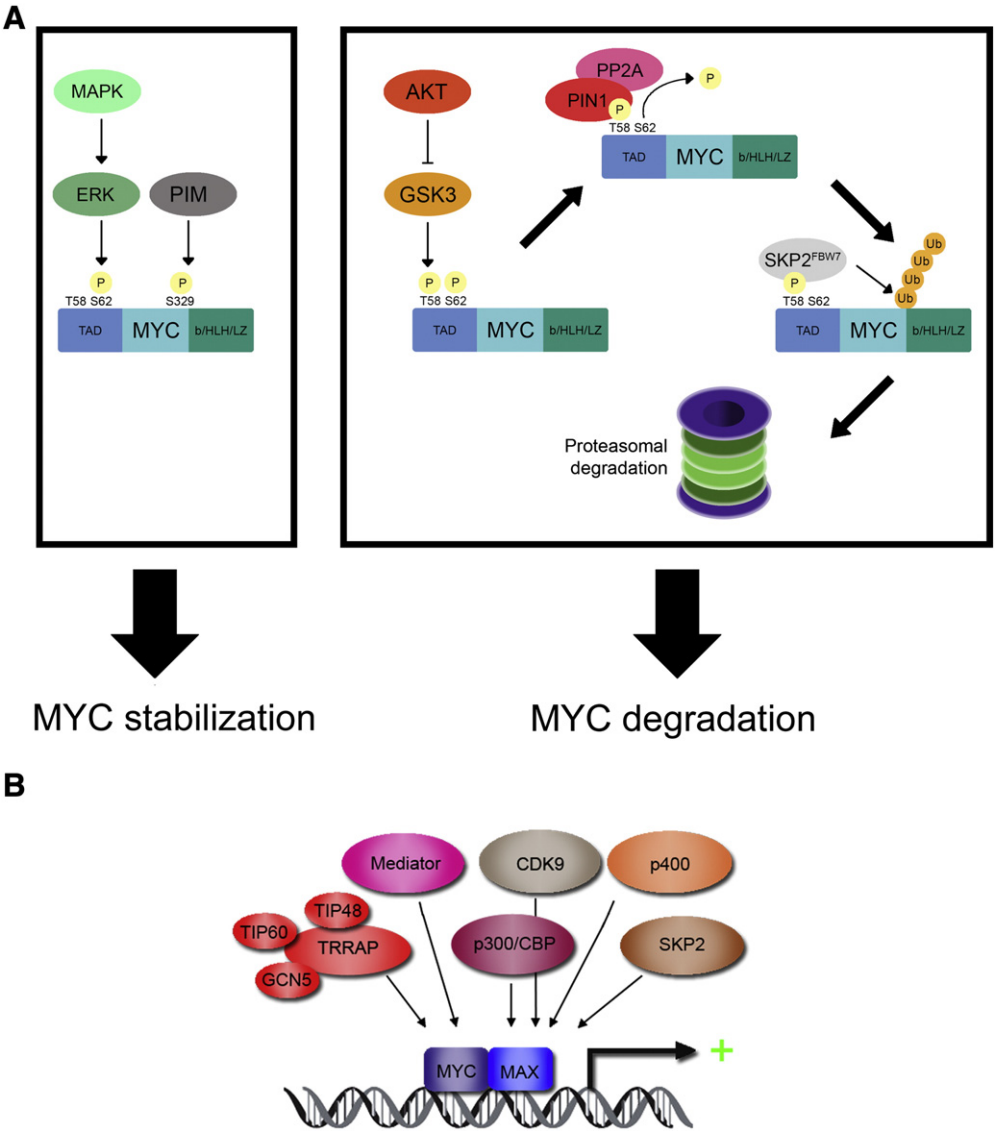

Fig. 1. Regulation of MYC activity. (A) Control of MYC stability and turnover. Mitogen-activated protein kinases stabilize MYC by phosphorylating Ser62. This modification facilitates subsequent phosphorylation of Thr58 by glycogen synthase kinase 3 (GSK3). Phosphorylated Thr58 serves as a platform for prolylisomerase1 (PIN1); modification of Pro59 enables phosphatase PP2A to remove phosphate residue from Ser62. $SKP2^{FBW7}$ E3 ubiquitin ligase then targets MYC for proteasomal degradation. PIM kinases stabilize MYC protein by phosphorylating Ser329 and altering the phosphorylation state of Thr58 and Ser62. (B) MYC binding partners enhancing MYC-dependent transcription. Upon binding to the E-box consensus sequence MYC-MAX, the heterodimer recruits several other proteins, such as Mediator complex, p300/CBP (CREB binding protein), TRRAP (transformation/transcription domain-associated protein), p400, SKP2 (S-phase kinase-associated protein 2, E3 ubiquitin protein ligase) and CDK9, which in turn can alter chromatin accessibility, modify transcription machinery or recruit other factors themselves (TIP60 (K[lysine]acetyltransferase 5), GCN5 (K acetyltransferase 2A), TIP48 (RuvB-like 2).

and lower-affinity E-boxes in the enhancer regions become engaged so further augmenting the transcriptional output [73,74].

The promoter output is commensurate with the amount of MYC loading, both in resting cells and in cells after mitogenic activation. The relationship between MYC DNA binding patterns and function therefore resembles a continuous (analog) process, rather than the binary switch often observed with other transcription factors [73]. Importantly, MYC exhibits similar functional characteristics in different cell types. In mouse embryonic stem (mES) cells, MYC was recruited to promoters with histone marks for open chromatin and MYC binding correlated with RNA polymerase II loading [73]. These observations suggests that MYC is preferentially associated with the transcription levels of active genes in cycling and quiescent cells.

These recent studies have changed the understanding of MYC biology and define a new model of physiological and oncogenic MYC function. In normal activated cells, transient pulses of MYC expression boost the biosynthetic and metabolic pathways to assure an appropriate supply of macromolecules in proliferating cells. Constitutive expression of high MYC levels in cancer engages lower affinity E-boxes in enhancers and pushes the expression of active cellular subsystems over critical thresholds, leaving the cell in the state of continuous proliferation and biosynthetic overdrive. Therefore, MYC increases fluxes through critical cellular networks and consolidates the cancer phenotype.

These findings, however, do not explain the mechanisms of MYC-mediated transcriptional repression. Given the previous studies estimating that even 1/3 of MYC targets are down-regulated, it is particularly important to reconcile these conflicting observations. Most likely, MYC-mediated transcriptional repression is indirect, as transcriptional or chromatin silencers activated by MYC are recruited to MYC target genes. For example, during B cell activation, MYC binds and up-regulates the EZH2 promoter; once overexpressed, EZH2 catalyzes methylation of histone H3 lysine 27 throughout the genome and suppresses transcription [73]. MYC can also interfere with transcriptional activation of zinc-finger transcription factors such as MIZ1 and SP1 [76]. Transcriptional repression is an important part of MYC oncogenic potential, as

multiple genes that are repressed by MYC encode negative regulators of cell proliferation or proteins involved in cell adhesion [76].

Since MYC amplifies fundamental cellular processes in cancer, certain aspects of its activity are common between different tumors featuring MYC over-expression and are interesting from the clinical and therapeutic standpoints. Specifically, MYC promotes transition from the G0/G1 to S phase of the cell cycle by increasing the expression of cyclins and cyclin dependent kinases (cyclin D–CDK4 and cyclin E–CDK2), resulting in hyperphosphorylation of retinoblastoma protein (RB1) and subsequent release of the E2F transcription factors responsible for cell cycle progression [77,78]. MYC also controls the G2/M checkpoint by increasing the expression of Cyclin B1, a component of the M-phase promoting factor, and increasing the expression of essential regulators of mitosis and cytokinesis, Aurora kinases A and B [79,80].

MYC (in cooperation with other transcription factors, e.g. HIF1α and HIF2), promotes the transcription of genes involved in glycolysis, eliciting the Warburg effect (enhanced anaerobic glycolysis independent of oxygen tension) [81]. The inherently lower energetic efficiency of glycolysis, compared to oxidative phosphorylation, and the decreased carbon flux to the tricarboxylic acid (TCA) cycle, is at least in part compensated by MYC and HIF-driven up-regulation of glucose transporters and thus enhanced glucose uptake [82]. MYC also increases glutaminolysis, sustaining supplementation of anabolic precursors to the TCA cycle and thereby providing an additional energy source. Under conditions of glucose deprivation, cancer cells over-expressing MYC depend on glutamine metabolism as its inhibition triggers apoptosis [83]. Furthermore, MYC increases the output of biosynthetic pathways for nucleotides, amino acids, polyamines, and phospholipids [84,85].

MYC also increases the expression of proapoptotic proteins, including over-expression of $p19^{ARF}$, suppression of MDM2 and activation of the p53 pathway [86,87]. In parallel to this, MYC induces the expression of the proapoptotic molecule BIM (BCL2-like 11) and indirectly represses the expression of anti-apoptotic BCL2 and BCL-XL (BCL2-like 1) proteins. Such mechanism likely represents a MYC self-imposed safety checkpoint, triggering programmed cell death in cells with prolonged MYC expression. Consistent with this, an increased expression of MYC in lymphoid malignancies is frequently accompanied by mutations of the p53 pathway, over-expression of anti-apoptotic factors and/or increased activity of alternative pro-survival pathways [88–90].

In addition to protein coding genes, MYC binds to regulatory sequences and modulates the expression of non-coding RNAs, including micro-RNAs (miRNAs). MYC represses multiple miRNAs, including tumor-suppressor miR-15a and miR-16, the let7 family, miR34a, miR-26a, miR-29, miR-150 and miR-195/miR-497 [91,92]. Although precise mechanisms of MYC-mediated repression of micro-RNAs remain elusive, recent studies highlight the role of MYC-dependent recruitment of histone modifying enzymes to regulatory elements of suppressed micro-RNAs. For example, in MCL, MYC recruits HDAC3 to the regulatory element of miR-15a/miR-16-1 or HDAC3 together with EZH2 (enhancer of zeste homolog 2) to miR-29 [93,94]. Furthermore, MYC contributes to the up-regulation of EZH2 via repressing EZH2-targeting miR-26a, thus creating a feed-forward loop, linking MYC-repressed microRNAs with this histone methyltransferase [93]. Consistent with the broad repression of tumor-suppressor micro-RNAs by MYC, forced over-expression of several of those repressed miRNAs have reduced MYC-induced lymphomagenesis in mouse xenograft models [92,95]. In addition to these specific effects, increased MYC level causes global down-regulation of micro-RNAs by perturbing their maturation [92,96]. On the other hand, MYC increases the expression of several oncogenic microRNAs ("oncomiRs"), including the micro-RNA cluster miR17-92, which contributes towards enhanced proliferation, survival, angiogenesis, metastasis and altered metabolism [97]. MYC-modulated miRNAs frequently target MYC-modulated proteins thus creating regulatory feed-forward circuits assuring a precise control over MYC-dependent biological effects [98]. Since a single micro-RNA can target multiple proteins, these regulatory circuits create complex networks that modulate MYC-dependent biological functions.

4. Synthetic lethal interactions of MYC

Over-expression of *Myc* transgene driven by immunoglobulin chain regulatory elements (Eμ *or IGL locus*) in mice leads to pre-B and B-cell lymphomas [5,6]. All tumors in these models were clonal, demonstrating that *MYC* transgene requires other lesions for tumor development. In line with these findings, numerous subsequent studies indicate that the viability and fitness of MYC over-expressing cells is reliant upon other genes and pathways, which may not be essential for normal cell survival or in the context of tumors driven by over-expression of other oncogenes. For these reasons, identification of these MYC "synthetic lethal" genes and pathways might facilitate therapeutic targeting of MYC-driven cancers.

Isolated over-expression of MYC triggers apoptosis, evoked by p53 response. In consistent fashion, tumors arising in Eμ-*Myc* transgenic mice have frequent alterations in the Arf-Mdm2-p53 tumor suppressor pathway [99]. Direct transcriptional targets of p53, BH3-only proteins Puma and Noxa, are important mediators of the proapoptotic effects of MYC, as the onset of Myc-induced lymphomas is accelerated by the knockout of *Puma* and mice with combined deficiency of *Puma* and *Noxa* produce lymphomas even more rapidly than those with loss of a single *Puma* allele alone [100–103]. Consistent with the proapoptotic effects of MYC over-expression, the onset of Myc-driven tumors is also accelerated by the loss of both alleles of the proapoptotic *Bax* (BCL2-associated X protein) gene. Moreover, $Bax^{-/-}$, Eμ-*Myc* transgenic mice were lacking *Tp53* alterations whereas 27% of the tumors in $Bax^{+/-}$ Eμ-*Myc* transgenic mice contained *Tp53* mutations or deletions, suggesting that the loss of *Bax* eliminates the selection for *Tp53* loss [103]. The onset of Eμ-*Myc* initiated tumors is also dramatically accelerated by the loss of single allele of another proapoptotic member of the Bcl2 family, *Bim* [86]. Up-regulation of Bcl2 similarly prevents Myc-induced apoptosis and potentiates oncogenic properties of the Eμ-*Myc* transgene [104,105]. Taken together, these observations demonstrate that in mouse models, tumors arising from MYC-over-expressing cells exhibit a selection for the loss of the p53 pathway and/or inactivation of apoptotic machinery. In keeping with this, inactivation of p53 is also observed in about 1/3 of the primary BL biopsies, over half of the BL cell lines and 2/3 of primary DLBCLs, highlighting the synthetic lethal interaction between MYC and the p53 pathway in the pathogenesis of human lymphomas [28,106,107]. Therefore, restoring or substituting the activity of proapoptotic effector mechanisms with BH3-mimetics is a rational strategy for disrupting these synthetic interactions. However, while the Bcl2 family members Bcl2, Bcl-XL, and Bcl-W are essential for Eμ-*Myc* induced lymphoma development, the genetic loss or inhibition of Bcl2, Bcl-XL, and Bcl-W has only a minimal impact on the growth of established tumors. Consistent with this, treatment of Eμ-*Myc* lymphomas with the BH3 mimetic ABT-737 targeting Bcl2, Bcl-XL, and Bcl-W does not cause tumor regression [108,109]. In contrast, sustained growth of Eμ-*Myc* lymphomas is dependent on Mcl1 since inducible, heterozygous deletion of *Mcl1* is sufficient to cause complete regression of these tumors. Importantly, the MCL1 blockade also efficiently kills human BL cell lines, independently of the p53 status [110].

MYC rearrangements to the immunoglobulin loci in BL involve exclusively non-productively rearranged alleles, indicating that BL cells are selected for B-cell receptor (BCR) expression. Given the essential role of the PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase) pathway in tonic BCR signaling and in providing anti-apoptotic/survival signals, recent studies have addressed the potential cooperation of MYC and the BCR-dependent PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase) pathway [111]. Reconstitution of $Rag2cg^{KO}$ mice (incapable of generating own lymphocytes), with bone marrow cells from *Myc*/*Pi3k* transgenic mice and over-expression of both genes in the GC environment have led to the development of monoclonal B-cell lymphomas,

whereas isolated over-expression of either transgene (*Myc* or *Pi3k*) did not result in any development of detectable tumors within the observation period. Furthermore, tumors arising from double transgenic cells phenocopy human BL in terms of the histology, cell surface markers and the profiles of protein expression [89].

Activation of PI3K pathway is also observed in human BL, especially in the sporadic subtype [88–90,112]. Increased activity of the PI3K pathway in these tumors is a result of either gain of function mutations of *TCF3* (transcription factor 3), or loss of function mutations of its negative regulator *ID3* (inhibitor of DNA binding 3), that augment the BCR signaling [88,90,112]. These mutations are observed in almost 70% of human sporadic BL samples [90]. In BL cells, TCF3 increases the expression of the BCR components and down-regulates expression of SHP-1 (protein tyrosine phosphatase, non-receptor type 6), leading to enhanced tonic BCR signaling and phospho-AKT levels [90].

Constitutive activity of TCF3 in BLs also induces the expression of cyclin D3, a positive regulator of early G1 transition, essential for GC reaction and cell cycle transition in normal germinal center lymphocytes [90,113,114]. Moreover, mutations stabilizing cyclin D3 and inactivating its inhibitor (p16) are found in up to 38% cases of sporadic BL and 67% of the HIV-associated subtype [89,90].

The PIM family of oncogenic kinases is another group of proteins potentiating and consolidating MYC-dependent lymphomagenesis. PIMs directly phosphorylate and stabilize the MYC protein, but also prevent MYC-induced apoptosis by phosphorylation and inactivation of the proapoptotic protein BAD (BCL2-associated agonist of cell death) [115]. In addition, at least one of three Pim kinases, Pim-3, is directly regulated by Myc via binding to one of the conserved E-boxes within the *Pim3* gene [116]. Over-expression of Myc and Pims in mouse pre-B cells resulted in rapid proliferation but also an inhibition of differentiation, whereas genetic or pharmaceutical inhibition of Pim kinases decreased the proliferation of cells over-expressing Myc [116–119].

5. Therapeutic targeting of MYC and its interactions

The essential role of MYC in multiple lymphoid tumors suggests that its targeted inactivation may be a rational and effective therapeutic strategy. In accord with this, inducible, ubiquitous over-expression of dominant-negative, recombinant MYC-derived basic helix-loop-helix leucine zipper domain termed OmoMYC in mice has led to significant inhibition of cancer progression, whereas there were no overt toxicities in most organs and tissues except for reversible growth retardation in skin, testis and the intestinal epithelium [120]. Furthermore, lymphomas over-expressing MYC are addicted to this oncogene as tumors recurring after prolonged MYC inactivation in a conditional transgenic mouse model of T-cell ALL, express either transgenic or endogenous MYC; albeit in many cases at levels below those in the original tumor [121]. Silencing MYC with shRNA elicited suppression of proliferation and increased apoptosis, confirming that these tumors remain oncogene-addicted. Taken together, targeting MYC is an attractive strategy for treating lymphomas featuring MYC over-expression and addiction [121], (Table 2).

Given the molecular mechanism of MYC action, the inhibition of its dimerization might be a rational approach for direct and specific intervention. However, although theoretically sound, the strategies targeting MYC association with its partners are difficult to develop practically, since MYC dimerization interfaces are large and featureless, without any pockets or clefts that could bind small molecules. Nonetheless, such compounds inhibiting MYC-MAX heterodimerization were obtained (e.g. 10058-F4 compound) and were demonstrated to prevent DNA binding and MYC-driven transcription *in vitro*. A similarly direct approach to disrupt the interaction of MYC with its binding partners is through the OmoMYC, which heterodimerizes with MYC, MAX and MIZ1 proteins and impedes MYC induced transactivation, induces cell cycle arrest, apoptosis and regression of mouse tumors [120,122,123]. Neither of these inhibitors has, however, reached the clinical trial stage, but both are available as “tool compounds”, providing the proof of principle that targeting MYC dimerization is feasible (Fig. 2) [124,125].

Recently, a novel class of inhibitors targeting BET bromodomain-containing proteins have been developed and are reported to interfere with MYC activity in certain tumors [126–129]. Bromodomains recognize acetylated lysines in histone tails and thus serve as organizers of the transcriptional machinery and activate transcription [128]. A member of the BET family, BRD4 exhibits highly asymmetric loading throughout the genomic regulatory elements, focusing predominantly on active genes' promoters and enhancers, particularly those with high levels of Mediator complex loading (“super-enhancers”) [129–132]. These super-enhancers are adjacent to cell fate determining master transcription factors [129–132]. For example, BRD4 binds avidly to *IgH* super-enhancer regulating MYC in MM cells and disruption of BRD4 association with this super-enhancer blocks MYC transcription, decreases MYC protein abundance, prompting cell-cycle arrest and cellular senescence [126,129,130,132]. Intriguingly, toxicity of BET

Table 2
Therapeutic approaches to target MYC-dependent tumors.

Strategy		Targets (compounds)	Mechanisms of action	Current research status
MYC dependent transcription		BET inhibition (JQ1, iBET, iBET151, CPI-0610, OTX015)	Abrogation of BRD4 DNA binding inhibits MYC-dependent pTEFb recruitment and transcription.	Phase I/II and I clinical trials (JQ1 derivative GSK525762, CPI-0610, OXT015)
MYC-MAX dimerization		MYC-MAX (10058-F4)	Inhibition of MYC-MAX dimerization prevents its binding to DNA and transcriptional activity.	Preclinical
MYC protein stability		PIM kinases (SMI-4a, Pimi, SGI-1776, AZD1208)	Inhibition of PIM kinase activity decreases MYC stability and its cellular abundance.	Phase I clinical trials (AZD1208)
MYC dependent cancer cell metabolism		LDHA (FX11), PDK1 (Dichloroacetate), MCT1 (AZD3965), GLUD1 (EGCG)	Inhibition of glycolysis and glutaminolysis leads to reduction of ATP levels, elevated ROS production and accumulation of toxic intermediates.	Phase I (AZD3965) and II (Dichloroacetate, EGCG) clinical trials
MYC synthetic lethal genes and pathways	Apoptosis	MCL1 and other BCL2 family members (BH3 mimetics)	Targeting prosurvival BCL2 family proteins restores proapoptotic properties of MYC.	Preclinical and phase I and II clinical trails
	Cell cycle	CDK4/6 (PD0332991), Aurora kinases (Alisertib, AT9283)	CDK and AURK inhibition induce cell cycle arrest and apoptosis.	Phase II clinical trials
	BCR signaling	PI3K (RP6530, BKM120), SYK (GS-9973, Fostamatinib) BTK (ibrutinib), AKT (MK2206, GSK2141795)	BCR/PI3K/AKT pathway inhibition.	Phase I (RP6530), II (BKM120, GS-9973, Fostamatinib, MK2206, GSK2141795) and III (ibrutinib) clinical trials

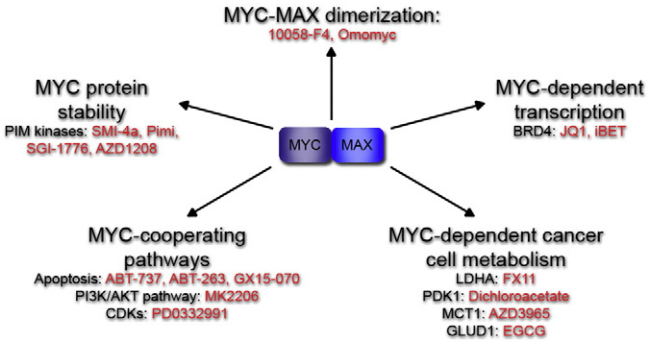

Fig. 2. Therapeutic strategies for targeting MYC-dependent tumors. See text for details.

inhibition in acute myeloid leukemia (AML), but not in DLBCL cells is averted by exogenous MYC expression, highlighting different super-enhancer associated dependencies in different tumors [129,133]. Utilizing different approaches, multiple selective compounds have been developed: JQ1, the iBET series, OTX015 and more recently – CPI-0610 [133–135]. These BET inhibitors abolish binding of the BRD4 coactivator to chromatin and suppress MYC-driven transcription in MYC-dependent tumor models. At the cellular level, bromodomain inhibitors induce tumor cell differentiation, cell cycle inhibition, senescence and exhibit cell-type dependent proapoptotic activity [126,129,136]. Bromodomain inhibitors caused tumor regression in mouse models of BL, AML, MM, mixed lineage leukemia (MLL) and DLBCL [126,127,136,137]. Of note, the mechanism of toxicity does not always involve MYC modulation, but also depends on the inhibition of other key genes regulated by BRD4-loaded super-enhancers. Recently, a BET bromodomain inhibitor I-BET762 (GSK525762) has entered clinical phase I/II trial in subjects with relapsed, refractory hematologic malignancies. CPI-0610 and OTX015 are tested in phase I clinical trials in patients with hematologic malignancies, including progressive lymphomas. Importantly, the CPI-0610 trial protocol includes assessing pharmacodynamic effects such as changes in the expression of MYC, changes in cellular proliferation and the extent of apoptosis.

Another strategy to target MYC-driven tumors is through inhibition of genes and pathways exhibiting "synthetic lethality" with this oncogene. MYC-driven tumors frequently over-express PIM kinases that directly phosphorylate and stabilize MYC protein and are potent enhancers of MYC-induced lymphomagenesis. Inhibition of PIM kinases decreases MYC abundance, cellular proliferation and induces apoptosis in BL, chronic lymphocytic leukemia (CLL) and AML cell lines [116,138,139]. Small molecule PIM inhibitors, (e.g. SMI-4a, Pimi and SGI-1776, AZD1208), show selective toxicity toward lymphoma cell lines *in vitro* [118]. Although phase I clinical trials for SGI-1776 indicate a dose limiting toxicity of cardiac QTc prolongation, the fact that mice deficient in Pim kinases exhibit mild/insignificant phenotypes, necessitates further research for more specific and safe strategies to target this kinase class [140].

Since abnormalities in the function of certain BCL2 family members are essential for MYC-driven lymphoma development and survival, the use of BH3-mimetics targeting members of the BCL2 family represents a further rational therapeutic strategy. Consistent with these observations, tumors from Eμ-*Myc*/*Bcl2* double transgenic mice were highly sensitive to ABT-737, a selective inhibitor of Bcl2, Bcl-XL and Bcl-W. However, studies on mouse Eμ-*Myc* lymphoma without concurrent transgenic Bcl2 expression indicate that ABT-737 is insufficient to eradicate established tumors due to the over-expression of Mcl1 [108,141]. Targeting Mcl1 with a different BH3-mimetic compound obatoclax (GX15-070), dramatically decreased the clonogenic potential and viability of BL cells from Eμ-*Myc* mice, underscoring the critical role of Mcl1 in antiapoptotic signaling in BL cells [108]. Since constitutive activity of PI3K/AKT/mTOR increases MCL1 expression, inhibition of this pathway represents another approach to eliminate this anti-apoptotic protein. Consistently, inhibition of PI3K/AKT/mTOR pathway reduces MCL1 expression levels and synergizes with ABT-737 in inducing apoptosis [142].

Another group of MYC-synthetic lethal genes are certain cell cycle kinases, such as cyclin-dependent kinases (*CCND3*) and Aurora kinases (*AURKA*, *AURKB*) [88,90,112]. Inhibition of cyclin D3/CDK4 and cyclin D3/CDK6 complexes, essential for cell cycle progression in BL and DLBCL cells with PD0332991 (a CKD4/6 inhibitor), induces cell cycle arrest followed by apoptosis in BL cell lines. PD0332991 caused complete tumor regression in BL xenograft models and is currently at phase II clinical trials for multiple malignancies [90,143]. In like fashion, blocking Aurka/b kinase activity with a specific inhibitor triggers transient mitotic arrest, polyploidization and apoptosis of murine Myc-induced lymphoma cells[79]. Importantly, apoptosis induced by Aurk inhibition was p53-independent, suggesting that inhibitors of these kinases might be of particular benefit in MYC-driven tumors featuring a loss of p53 function [79]. In a recently completed phase II clinical trial of a selective Aurora A kinase inhibitor, alisertib, the overall response rate in lymphoma patients was 27%, including responses in three out of 21 patients with DLBCL, a BL patient and a transformed follicular lymphoma patient with "double-hit" features in an immunochemical assessment [144].

Parallel to targeting MYC and associated signaling pathways, there are ongoing efforts to develop therapies altering MYC-dependent cancer cell metabolism. MYC up-regulates the majority of genes involved in glycolysis and glutaminolysis. Inhibiting many of these enzymes induce apoptosis and impair MYC-induced lymphoma growth in preclinical studies. Although inhibitors of upstream glycolytic enzymes (e.g. hexokinase inhibitors 2-deoxy-D-glucose and lonidamine) failed clinical trials on solid tumors due to toxicity, there are several other compounds targeting glucose metabolism in MYC-over-expressing cells, awaiting confirmation of their clinical utility (Table 2). For instance, inhibition of lactate dehydrogenase A (LDHA) by FX11 elevates ROS production, reduces ATP levels, promotes cell death and inhibits progression of MYC-dependent lymphoma xenografts [145]. Accumulation of lactate caused by the inhibition of monocaroboxylate transporter 1 (MCT1, SLC16A1) with a specific inhibitor AZD3965 lowers cellular pH, inhibits glycolysis and reduces lymphoma xenograft growth [146]. Targeting pyruvate dehydrogenase kinase 1 (PDK1) by dichloroacetate (DCA) switches the carbon flux from glycolysis to glucose oxidation, elevates ROS production and decreases the inner mitochondrial membrane potential sensitizing cells to apoptosis and blocking tumor growth [147,148]. Inhibition of glutamine metabolism by the glutamate dehydrogenase 1 (GLUD1) inhibitor EGCG, induces proapoptotic proteins leading to cell apoptosis and reduced lymphoma model growth [149]. AZD3965 and EGCG are undergoing clinical trials in DLBCL (phase I) and MM (phase II) patients.

5.1. Summary and future directions

Studies explaining MYC function and the cooperative events during MYC-induced lymphomagenesis have provided new insights into the biology of these tumors, but also opened new possibilities for targeting MYC. In line with a relatively deep and thorough knowledge for explaining MYC structure, binding partners and molecular function, we are now witnessing the first trials in bringing newly developed compounds to clinical testing. Most clinical studies evaluating new compounds targeting MYC focus on solid tumors, while trials evaluating the effectiveness of such therapies specifically in lymphoid malignancies with MYC addiction are lacking. The clinical utility of strategies targeting MYC for this patient group therefore remains to be defined. As MYC research enters the phase of high-throughput analyses coupled to structural and biological testing, these studies hold promise for new, rationally designed and specific drugs inhibiting the function of this oncogene and the cooperating pathways. Sensible choice of compounds that can advance to the clinical development phase, careful planning

of study protocols and proper inclusion of clinical biomarkers are becoming crucial for future successful outcomes.

Acknowledgements

This work and T.S. PhD scholarship are supported by a Foundation for Polish Science grant TEAM/2011-7/4, co-financed by the European Regional Development Fund and Operational Program Innovative Economy 2007–2013.

References

[1] D. Sheiness, J.M. Bishop, DNA and RNA from uninfected vertebrate cells contain nucleotide sequences related to the putative transforming gene of avian myelocytomatosis virus, J. Virol. 31 (1979) 514–521.
[2] H.E. Varmus, The molecular genetics of cellular oncogenes, Annu. Rev. Genet. 18 (1984) 553–612.
[3] R. Dalla-Favera, M. Bregni, J. Erikson, D. Patterson, R.C. Gallo, C.M. Croce, Human c-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells, Proc. Natl. Acad. Sci. U. S. A. 79 (1982) 7824–7827.
[4] R. Taub, I. Kirsch, C. Morton, G. Lenoir, D. Swan, S. Tronick, S. Aaronson, P. Leder, Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells, Proc. Natl. Acad. Sci. U. S. A. 79 (1982) 7837–7841.
[5] J.M. Adams, A.W. Harris, C.A. Pinkert, L.M. Corcoran, W.S. Alexander, S. Cory, R.D. Palmiter, R.L. Brinster, The c-myc oncogene driven by immunoglobulin enhancers induces lymphoid malignancy in transgenic mice, Nature 318 (1985) 533–538.
[6] A.L. Kovalchuk, C.F. Qi, T.A. Torrey, L. Taddesse-Heath, L. Feigenbaum, S.S. Park, A. Gerbitz, G. Klobeck, K. Hoertnagel, A. Polack, G.W. Bornkamm, S. Janz, H.C. Morse III, Burkitt lymphoma in the mouse, J. Exp. Med. 192 (2000) 1183–1190.
[7] T.A. Baudino, C. McKay, H. Pendeville-Samain, J.A. Nilsson, K.H. Maclean, E.L. White, A.C. Davis, J.N. Ihle, J.L. Cleveland, c-Myc is essential for vasculogenesis and angiogenesis during development and tumor progression, Genes Dev. 16 (2002) 2530–2543.
[8] A. Wilson, M.J. Murphy, T. Oskarsson, K. Kaloulis, M.D. Bettess, G.M. Oser, A.C. Pasche, C. Knabenhans, H.R. Macdonald, A. Trumpp, c-Myc controls the balance between hematopoietic stem cell self-renewal and differentiation, Genes Dev. 18 (2004) 2747–2763.
[9] E. Baena, M. Ortiz, A.C. Martinez, I.M. de Alboran, c-Myc is essential for hematopoietic stem cell differentiation and regulates Lin(−)Sca-1(+)c-Kit(−) cell generation through p21, Exp. Hematol. 35 (2007) 1333–1343.
[10] C.Y. Huang, A.L. Bredemeyer, L.M. Walker, C.H. Bassing, B.P. Sleckman, Dynamic regulation of c-Myc proto-oncogene expression during lymphocyte development revealed by a GFP-c-Myc knock-in mouse, Eur. J. Immunol. 38 (2008) 342–349.
[11] D. Dominguez-Sola, G.D. Victora, C.Y. Ying, R.T. Phan, M. Saito, M.C. Nussenzweig, R. Dalla-Favera, The proto-oncogene MYC is required for selection in the germinal center and cyclic reentry, Nat. Immunol. 13 (2012) 1083–1091.
[12] Y. Lin, K. Wong, K. Calame, Repression of c-myc transcription by Blimp-1, an inducer of terminal B cell differentiation, Science (New York, N.Y.) 276 (1997) 596–599.
[13] D.P. Calado, Y. Sasaki, S.A. Godinho, A. Pellerin, K. Kochert, B.P. Sleckman, I.M. de Alboran, M. Janz, S. Rodig, K. Rajewsky, The cell-cycle regulator c-Myc is essential for the formation and maintenance of germinal centers, Nat. Immunol. 13 (2012) 1092–1100.
[14] D.F. Robbiani, A. Bothmer, E. Callen, B. Reina-San-Martin, Y. Dorsett, S. Difilippantonio, D.J. Bolland, H.T. Chen, A.E. Corcoran, A. Nussenzweig, M.C. Nussenzweig, AID is required for the chromosomal breaks in c-myc that lead to c-myc/IgH translocations, Cell 135 (2008) 1028–1038.
[15] A.R. Ramiro, M. Jankovic, T. Eisenreich, S. Difilippantonio, S. Chen-Kiang, M. Muramatsu, T. Honjo, A. Nussenzweig, M.C. Nussenzweig, AID is required for c-myc/IgH chromosome translocations in vivo, Cell 118 (2004) 431–438.
[16] O. Balague Ponz, G. Ott, R.P. Hasserjian, K.S. Elenitoba-Johnson, L. de Leval, D. de Jong, Commentary on the WHO classification of tumors of lymphoid tissues (2008): aggressive B-cell lymphomas, J. Hematop. 2 (2009) 83–87.
[17] L. Leoncini, M. Raphaël, H. Stein, N.L. Harris, E.S. Jaffe, Burkitt lymphoma, in: S.H. Swerdlow, E. Campo, N.L. Harris, E.S. Jaffe, S.A. Pileri, H. Stein, J. Thiele, J.W. Varidman (Eds.), WHO classification of tumours of haematopoietic and lymphoid tissues, IARC, Lyon, France, 2008, pp. 262–264.
[18] A. Dogan, E. Bagdi, P. Munson, P.G. Isaacson, CD10 and BCL-6 expression in paraffin sections of normal lymphoid tissue and B-cell lymphomas, Am. J. Surg. Pathol. 24 (2000) 846–852.
[19] E.G. Boerma, R. Siebert, P.M. Kluin, M. Baudis, Translocations involving 8q24 in Burkitt lymphoma and other malignant lymphomas: a historical review of cytogenetics in the light of todays knowledge, Leuk. Off. J. Leuk. Soc. Am. Leuk. Res. Fund UK 23 (2009) 225–234.
[20] A. Neri, F. Barriga, D.M. Knowles, I.T. Magrath, R. Dalla-Favera, Different regions of the immunoglobulin heavy-chain locus are involved in chromosomal translocations in distinct pathogenetic forms of Burkitt lymphoma, Proc. Natl. Acad. Sci. U. S. A. 85 (1988) 2748–2752.
[21] B. Morse, V.J. South, P.G. Rothberg, S.M. Astrin, Somatic mutation and transcriptional deregulation of myc in endemic Burkitt's lymphoma disease: heptamer-nonamer recognition mistakes? Mol. Cell. Biol. 9 (1989) 74–82.
[22] D. de Jong, O. Balague Ponz, The molecular background of aggressive B cell lymphomas as a basis for targeted therapy, J. Pathol. 223 (2011) 274–282.
[23] E. Leucci, M. Cocco, A. Onnis, G. De Falco, P. van Cleef, C. Bellan, A. van Rijk, J. Nyagol, B. Byakika, S. Lazzi, P. Tosi, H. van Krieken, L. Leoncini, MYC translocation-negative classical Burkitt lymphoma cases: an alternative pathogenetic mechanism involving miRNA deregulation, J. Pathol. 216 (2008) 440–450.
[24] A. Onnis, G. De Falco, G. Antonicelli, M. Onorati, C. Bellan, O. Sherman, S. Sayed, L. Leoncini, Alteration of microRNAs regulated by c-Myc in Burkitt lymphoma, PLoS One 5 (2010).
[25] I. Salaverria, I. Martin-Guerrero, R. Wagener, M. Kreuz, C.W. Kohler, J. Richter, B. Pienkowska-Grela, P. Adam, B. Burkhardt, A. Claviez, C. Damm-Welk, H.G. Drexler, M. Hummel, E.S. Jaffe, R. Kuppers, C. Lefebvre, J. Lisfeld, M. Loffler, R.A. Macleod, I. Nagel, I. Oschlies, M. Rosolowski, R.B. Russell, G. Rymkiewicz, D. Schindler, M. Schlesner, R. Scholtysik, C. Schwaenen, R. Spang, M. Szczepanowski, L. Trumper, I. Vater, S. Wessendorf, W. Klapper, R. Siebert, A recurrent 11q aberration pattern characterizes a subset of MYC-negative high-grade B-cell lymphomas resembling Burkitt lymphoma, Blood 123 (2014) 1187–1198.
[26] J.O. Armitage, D.D. Weisenburger, New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 16 (1998) 2780–2795.
[27] N. Tomita, BCL2 and MYC dual-hit lymphoma/leukemia, J. clin. exp. Hematopathology: JCEH 51 (2011) 7–12.
[28] S. Monti, B. Chapuy, K. Takeyama, S.J. Rodig, Y. Hao, K.T. Yeda, H. Inguilizian, C. Mermel, T. Currie, A. Dogan, J.L. Kutok, R. Beroukhim, D. Neuberg, T.M. Habermann, G. Getz, A.L. Kung, T.R. Golub, M.A. Shipp, Integrative analysis reveals an outcome-associated and targetable pattern of p53 and cell cycle deregulation in diffuse large B cell lymphoma, Cancer Cell 22 (2012) 359–372.
[29] C.J. Stasik, H. Nitta, W. Zhang, C.H. Mosher, J.R. Cook, R.R. Tubbs, J.M. Unger, T.A. Brooks, D.O. Persky, S.T. Wilkinson, T.M. Grogan, L.M. Rimsza, Increased MYC gene copy number correlates with increased mRNA levels in diffuse large B-cell lymphoma, Haematologica 95 (2010) 597–603.
[30] M. Hummel, S. Bentink, H. Berger, W. Klapper, S. Wessendorf, T.F. Barth, H.W. Bernd, S.B. Cogliatti, J. Dierlamm, A.C. Feller, M.L. Hansmann, E. Haralambieva, L. Harder, D. Hasenclever, M. Kuhn, D. Lenze, P. Lichter, J.I. Martin-Subero, P. Moller, H.K. Muller-Hermelink, G. Ott, R.M. Parwaresch, C. Pott, A. Rosenwald, M. Rosolowski, C. Schwaenen, B. Sturzenhofecker, M. Szczepanowski, H. Trautmann, H.H. Wacker, R. Spang, M. Loeffler, L. Trumper, H. Stein, R. Siebert, K. Molecular, Mechanisms in Malignant Lymphomas Network Project of the Deutsche, a biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling, N. Engl. J. Med. 354 (2006) 2419–2430.
[31] S.M. Aukema, R. Siebert, E. Schuuring, G.W. van Imhoff, H.C. Kluin-Nelemans, E.J. Boerma, P.M. Kluin, Double-hit B-cell lymphomas, Blood 117 (2011) 2319–2331.
[32] H. Horn, M. Ziepert, C. Becher, T.F. Barth, H.W. Bernd, A.C. Feller, W. Klapper, M. Hummel, H. Stein, M.L. Hansmann, C. Schmelter, P. Moller, S. Cogliatti, M. Pfreundschuh, N. Schmitz, L. Trumper, R. Siebert, M. Loeffler, A. Rosenwald, G. Ott, MYC status in concert with BCL2 and BCL6 expression predicts outcome in diffuse large B-cell lymphoma, Blood 121 (2013) 2253–2263.
[33] S.S. Dave, K. Fu, G.W. Wright, L.T. Lam, P. Kluin, E.J. Boerma, T.C. Greiner, D.D. Weisenburger, A. Rosenwald, G. Ott, H.K. Muller-Hermelink, R.D. Gascoyne, J. Delabie, L.M. Rimsza, R.M. Braziel, T.M. Grogan, E. Campo, E.S. Jaffe, B.J. Dave, W. Sanger, M. Bast, J.M. Vose, J.O. Armitage, J.M. Connors, E.B. Smeland, S. Kvaloy, H. Holte, R.I. Fisher, T.P. Miller, E. Montserrat, W.H. Wilson, M. Bahl, H. Zhao, L. Yang, J. Powell, R. Simon, W.C. Chan, L.M. Staudt, Molecular diagnosis of Burkitt's lymphoma, N. Engl. J. Med. 354 (2006) 2431–2442.
[34] M.J. Kluk, B. Chapuy, P. Sinha, A. Roy, P. Dal Cin, D.S. Neuberg, S. Monti, G.S. Pinkus, M.A. Shipp, S.J. Rodig, Immunohistochemical detection of MYC-driven diffuse large B-cell lymphomas, PLoS One 7 (2012) e33813.
[35] S. Hu, Z.Y. Xu-Monette, A. Tzankov, T. Green, L. Wu, A. Balasubramanyam, W.M. Liu, C. Visco, Y. Li, R.N. Miranda, S. Montes-Moreno, K. Dybkaer, A. Chiu, A. Orazi, Y. Zu, G. Bhagat, K.L. Richards, E.D. Hsi, W.W. Choi, X. Zhao, J.H. van Krieken, Q. Huang, J. Huh, W. Ai, M. Ponzoni, A.J. Ferreri, F. Zhou, G.W. Slack, R.D. Gascoyne, M. Tu, D. Variakojis, W. Chen, R.S. Go, M.A. Piris, M.B. Moller, L.J. Medeiros, K.H. Young, MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program, Blood 121 (2013) 4021–4031 (quiz 4250).
[36] A. Valera, A. Lopez-Guillermo, T. Cardesa-Salzmann, F. Climent, E. Gonzalez-Barca, S. Mercadal, I. Espinosa, S. Novelli, J. Briones, J.L. Mate, O. Salamero, J.M. Sancho, L. Arenillas, S. Serrano, N. Erill, D. Martinez, P. Castillo, J. Rovira, A. Martinez, E. Campo, L. Colomo, MYC protein expression and genetic alterations have prognostic impact in patients with diffuse large B-cell lymphoma treated with immunochemotherapy, Haematologica 98 (2013) 1554–1562.
[37] R.F. McClure, E.D. Remstein, W.R. Macon, G.W. Dewald, T.M. Habermann, A. Hoering, P.J. Kurtin, Adult B-cell lymphomas with burkitt-like morphology are phenotypically and genotypically heterogeneous with aggressive clinical behavior, Am. J. Surg. Pathol. 29 (2005) 1652–1660.
[38] E. Haralambieva, E.J. Boerma, G.W. van Imhoff, S. Rosati, E. Schuuring, H.K. Muller-Hermelink, P.M. Kluin, G. Ott, Clinical, immunophenotypic, and genetic analysis of adult lymphomas with morphologic features of Burkitt lymphoma, Am. J. Surg. Pathol. 29 (2005) 1086–1094.
[39] P.M. Kluin, N.L. Harris, H. Stein, L. Leoncini, M. Raphaël, E. Campo, E.S. Jaffe, B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, in: S.H. Swerdlow, E. Campo, N.L. Harris, E.S. Jaffe, S.A. Pileri, H. Stein, J. Thiele, J.W. Varidman (Eds.), WHO classification of tumours of haematopoietic and lymphoid tissues, IARC, Lyon, France, 2008, pp. 265–266.

[40] W. Klapper, H. Stoecklein, S. Zeynalova, G. Ott, F. Kosari, A. Rosenwald, M. Loeffler, L. Trumper, M. Pfreundschuh, R. Siebert, German high-grade non-Hodgkin's lymphoma study, structural aberrations affecting the MYC locus indicate a poor prognosis independent of clinical risk factors in diffuse large B-cell lymphomas treated within randomized trials of the German high-grade non-Hodgkin's lymphoma study group (DSHNHL), Leuk. Off. J. Leuk. Soc. Am. Leuk. Res. Fund UK 22 (2008) 2226–2229.
[41] K.J. Savage, N.A. Johnson, S. Ben-Neriah, J.M. Connors, L.H. Sehn, P. Farinha, D.E. Horsman, R.D. Gascoyne, MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy, Blood 114 (2009) 3533–3537.
[42] S. Barrans, S. Crouch, A. Smith, K. Turner, R. Owen, R. Patmore, E. Roman, A. Jack, Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 28 (2010) 3360–3365.
[43] T.M. Green, K.H. Young, C. Visco, Z.Y. Xu-Monette, A. Orazi, R.S. Go, O. Nielsen, O.V. Gadeberg, T. Mourits-Andersen, M. Frederiksen, L.M. Pedersen, M.B. Moller, Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 30 (2012) 3460–3467.
[44] N.A. Johnson, K.J. Savage, O. Ludkovski, S. Ben-Neriah, R. Woods, C. Steidl, M.J. Dyer, R. Siebert, J. Kuruvilla, R. Klasa, J.M. Connors, R.D. Gascoyne, D.E. Horsman, Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival, Blood 114 (2009) 2273–2279.
[45] M.D. Delgado, J. Leon, Myc roles in hematopoiesis and leukemia, Genes Cancer 1 (2010) 605–616.
[46] A. Valera, O. Balague, L. Colomo, A. Martinez, J. Delabie, L. Taddesse-Heath, E.S. Jaffe, E. Campo, IG/MYC rearrangements are the main cytogenetic alteration in plasmablastic lymphomas, Am. J. Surg. Pathol. 34 (2010) 1686–1694.
[47] S.M. Smith, J. Anastasi, K.S. Cohen, L.A. Godley, The impact of MYC expression in lymphoma biology: beyond Burkitt lymphoma, Blood Cells Mol. Dis. 45 (2010) 317–323.
[48] E.M. Blackwood, R.N. Eisenman, Max: a helix-loop-helix zipper protein that forms a sequence-specific DNA-binding complex with Myc, Science (New York, N.Y.) 251 (1991) 1211–1217.
[49] C. Dani, J.M. Blanchard, M. Piechaczyk, S. El Sabouty, L. Marty, P. Jeanteur, Extreme instability of myc mRNA in normal and transformed human cells, Proc. Natl. Acad. Sci. U. S. A. 81 (1984) 7046–7050.
[50] S.R. Hann, R.N. Eisenman, Proteins encoded by the human c-myc oncogene: differential expression in neoplastic cells, Mol. Cell. Biol. 4 (1984) 2486–2497.
[51] E. Yeh, M. Cunningham, H. Arnold, D. Chasse, T. Monteith, G. Ivaldi, W.C. Hahn, P.T. Stukenberg, S. Shenolikar, T. Uchida, C.M. Counter, J.R. Nevins, A.R. Means, R. Sears, A signalling pathway controlling c-Myc degradation that impacts oncogenic transformation of human cells, Nat. Cell Biol. 6 (2004) 308–318.
[52] M.A. Gregory, Y. Qi, S.R. Hann, Phosphorylation by glycogen synthase kinase-3 controls c-myc proteolysis and subnuclear localization, J. Biol. Chem. 278 (2003) 51606–51612.
[53] Y. Zhang, Z. Wang, X. Li, N.S. Magnuson, Pim kinase-dependent inhibition of c-Myc degradation, Oncogene 27 (2008) 4809–4819.
[54] S. Kanazawa, L. Soucek, G. Evan, T. Okamoto, B.M. Peterlin, c-Myc recruits P-TEFb for transcription, cellular proliferation and apoptosis, Oncogene 22 (2003) 5707–5711.
[55] J. Vervoorts, J.M. Luscher-Firzlaff, S. Rottmann, R. Lilischkis, G. Walsemann, K. Dohmann, M. Austen, B. Luscher, Stimulation of c-MYC transcriptional activity and acetylation by recruitment of the cofactor CBP, EMBO Rep. 4 (2003) 484–490.
[56] S.R. Frank, M. Schroeder, P. Fernandez, S. Taubert, B. Amati, Binding of c-Myc to chromatin mediates mitogen-induced acetylation of histone H4 and gene activation, Genes Dev. 15 (2001) 2069–2082.
[57] M.A. Wood, S.B. McMahon, M.D. Cole, An ATPase/helicase complex is an essential cofactor for oncogenic transformation by c-Myc, Mol. Cell 5 (2000) 321–330.
[58] M. Fuchs, J. Gerber, R. Drapkin, S. Sif, T. Ikura, V. Ogryzko, W.S. Lane, Y. Nakatani, D.M. Livingston, The p400 complex is an essential E1A transformation target, Cell 106 (2001) 297–307.
[59] N. von der Lehr, S. Johansson, S. Wu, F. Bahram, A. Castell, C. Cetinkaya, P. Hydbring, I. Weidung, K. Nakayama, K.I. Nakayama, O. Soderberg, T.K. Kerppola, L.G. Larsson, The F-box protein Skp2 participates in c-Myc proteosomal degradation and acts as a cofactor for c-Myc-regulated transcription, Mol. Cell 11 (2003) 1189–1200.
[60] P. Staller, K. Peukert, A. Kiermaier, J. Seoane, J. Lukas, H. Karsunky, T. Moroy, J. Bartek, J. Massague, F. Hanel, M. Eilers, Repression of p15INK4b expression by Myc through association with Miz-1, Nat. Cell Biol. 3 (2001) 392–399.
[61] C. Brenner, R. Deplus, C. Didelot, A. Loriot, E. Vire, C. De Smet, A. Gutierrez, D. Danovi, D. Bernard, T. Boon, P.G. Pelicci, B. Amati, T. Kouzarides, Y. de Launoit, L. Di Croce, F. Fuks, Myc represses transcription through recruitment of DNA methyltransferase corepressor, EMBO J. 24 (2005) 336–346.
[62] P.J. Hurlin, C. Queva, P.J. Koskinen, E. Steingrimsson, D.E. Ayer, N.G. Copeland, N.A. Jenkins, R.N. Eisenman, Mad3 and Mad4: novel Max-interacting transcriptional repressors that suppress c-myc dependent transformation and are expressed during neural and epidermal differentiation, EMBO J. 14 (1995) 5646–5659.
[63] P.J. Hurlin, C. Queva, R.N. Eisenman, Mnt, a novel Max-interacting protein is coexpressed with Myc in proliferating cells and mediates repression at Myc binding sites, Genes Dev. 11 (1997) 44–58.
[64] C.A. Hassig, T.C. Fleischer, A.N. Billin, S.L. Schreiber, D.E. Ayer, Histone deacetylase activity is required for full transcriptional repression by mSin3A, Cell 89 (1997) 341–347.
[65] K. Berns, E.M. Hijmans, E. Koh, G.Q. Daley, R. Bernards, A genetic screen to identify genes that rescue the slow growth phenotype of c-myc null fibroblasts, Oncogene 19 (2000) 3330–3334.
[66] M.A. Nikiforov, S. Chandriani, B. O'Connell, O. Petrenko, I. Kotenko, A. Beavis, J.M. Sedivy, M.D. Cole, A functional screen for Myc-responsive genes reveals serine hydroxymethyltransferase, a major source of the one-carbon unit for cell metabolism, Mol. Cell. Biol. 22 (2002) 5793–5800.
[67] A.L. Shaffer, G. Wright, L. Yang, J. Powell, V. Ngo, L. Lamy, L.T. Lam, R.E. Davis, L.M. Staudt, A library of gene expression signatures to illuminate normal and pathological lymphoid biology, Immunol. Rev. 210 (2006) 67–85.
[68] A.A. Margolin, T. Palomero, P. Sumazin, A. Califano, A.A. Ferrando, G. Stolovitzky, ChIP-on-chip significance analysis reveals large-scale binding and regulation by human transcription factor oncogenes, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 244–249.
[69] I. Ben-Porath, M.W. Thomson, V.J. Carey, R. Ge, G.W. Bell, A. Regev, R.A. Weinberg, An embryonic stem cell-like gene expression signature in poorly differentiated aggressive human tumors, Nat. Genet. 40 (2008) 499–507.
[70] K. Ellwood-Yen, T.G. Graeber, J. Wongvipat, M.L. Iruela-Arispe, J. Zhang, R. Matusik, G.V. Thomas, C.L. Sawyers, Myc-driven murine prostate cancer shares molecular features with human prostate tumors, Cancer Cell 4 (2003) 223–238.
[71] S. Adhikary, M. Eilers, Transcriptional regulation and transformation by Myc proteins, Nat. Rev. Mol. Cell Biol. 6 (2005) 635–645.
[72] J.H. Patel, A.P. Loboda, M.K. Showe, L.C. Showe, S.B. McMahon, Analysis of genomic targets reveals complex functions of MYC, Nat. Rev. Cancer 4 (2004) 562–568.
[73] Z. Nie, G. Hu, G. Wei, K. Cui, A. Yamane, W. Resch, R. Wang, D.R. Green, L. Tessarollo, R. Casellas, K. Zhao, D. Levens, c-Myc is a universal amplifier of expressed genes in lymphocytes and embryonic stem cells, Cell 151 (2012) 68–79.
[74] C.Y. Lin, J. Loven, P.B. Rahl, R.M. Paranal, C.B. Burge, J.E. Bradner, T.I. Lee, R.A. Young, Transcriptional amplification in tumor cells with elevated c-Myc, Cell 151 (2012) 56–67.
[75] P.B. Rahl, C.Y. Lin, A.C. Seila, R.A. Flynn, S. McCuine, C.B. Burge, P.A. Sharp, R.A. Young, c-Myc regulates transcriptional pause release, Cell 141 (2010) 432–445.
[76] B. Herkert, M. Eilers, Transcriptional repression: the dark side of myc, Genes Cancer 1 (2010) 580–586.
[77] P. Steiner, A. Philipp, J. Lukas, D. Godden-Kent, M. Pagano, S. Mittnacht, J. Bartek, M. Eilers, Identification of a Myc-dependent step during the formation of active G1 cyclin-cdk complexes, EMBO J. 14 (1995) 4814–4826.
[78] R.L. Beijersbergen, R. Bernards, Cell cycle regulation by the retinoblastoma family of growth inhibitory proteins, Biochim. Biophys. Acta 1287 (1996) 103–120.
[79] J. den Hollander, S. Rimpi, J.R. Doherty, M. Rudelius, A. Buck, A. Hoellein, M. Kremer, N. Graf, M. Scheerer, M.A. Hall, A. Goga, N. von Bubnoff, J. Duyster, C. Peschel, J.L. Cleveland, J.A. Nilsson, U. Keller, Aurora kinases A and B are up-regulated by Myc and are essential for maintenance of the malignant state, Blood 116 (2010) 1498–1505.
[80] A. Menssen, H. Hermeking, Characterization of the c-MYC-regulated transcriptome by SAGE: identification and analysis of c-MYC target genes, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 6274–6279.
[81] O. Warburg, On the origin of cancer cells, Science (New York, N.Y.) 123 (1956) 309–314.
[82] R.C. Osthus, H. Shim, S. Kim, Q. Li, R. Reddy, M. Mukherjee, Y. Xu, D. Wonsey, L.A. Lee, C.V. Dang, Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc, J. Biol. Chem. 275 (2000) 21797–21800.
[83] A. Le, A.N. Lane, M. Hamaker, S. Bose, A. Gouw, J. Barbi, T. Tsukamoto, C.J. Rojas, B.S. Slusher, H. Zhang, L.J. Zimmerman, D.C. Liebler, R.J. Slebos, P.K. Lorkiewicz, R.M. Higashi, T.W. Fan, C.V. Dang, Glucose-independent glutamine metabolism via TCA cycling for proliferation and survival in B cells, Cell Metab. 15 (2012) 110–121.
[84] J.D. Gordan, C.B. Thompson, M.C. Simon, HIF and c-Myc: sibling rivals for control of cancer cell metabolism and proliferation, Cancer Cell 12 (2007) 108–113.
[85] B.C. O'Connell, A.F. Cheung, C.P. Simkevich, W. Tam, X. Ren, M.K. Mateyak, J.M. Sedivy, A large scale genetic analysis of c-Myc-regulated gene expression patterns, J. Biol. Chem. 278 (2003) 12563–12573.
[86] A. Egle, A.W. Harris, P. Bouillet, S. Cory, Bim is a suppressor of Myc-induced mouse B cell leukemia, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 6164–6169.
[87] F. Zindy, C.M. Eischen, D.H. Randle, T. Kamijo, J.L. Cleveland, C.J. Sherr, M.F. Roussel, Myc signaling via the ARF tumor suppressor regulates p53-dependent apoptosis and immortalization, Genes Dev. 12 (1998) 2424–2433.
[88] C. Love, Z. Sun, D. Jima, G. Li, J. Zhang, R. Miles, K.L. Richards, C.H. Dunphy, W.W. Choi, G. Srivastava, P.L. Lugar, D.A. Rizzieri, A.S. Lagoo, L. Bernal-Mizrachi, K.P. Mann, C.R. Flowers, K.N. Naresh, A.M. Evens, A. Chadburn, L.I. Gordon, M.B. Czader, J.I. Gill, E.D. Hsi, A. Greenough, A.B. Moffitt, M. McKinney, A. Banerjee, V. Grubor, S. Levy, D.B. Dunson, S.S. Dave, The genetic landscape of mutations in Burkitt lymphoma, Nat. Genet. 44 (2012) 1321–1325.
[89] S. Sander, D.P. Calado, L. Srinivasan, K. Kochert, B. Zhang, M. Rosolowski, S.J. Rodig, K. Holzmann, S. Stilgenbauer, R. Siebert, L. Bullinger, K. Rajewsky, Synergy between PI3K signaling and MYC in Burkitt lymphomagenesis, Cancer Cell 22 (2012) 167–179.
[90] R. Schmitz, R.M. Young, M. Ceribelli, S. Jhavar, W. Xiao, M. Zhang, G. Wright, A.L. Shaffer, D.J. Hodson, E. Buras, X. Liu, J. Powell, Y. Yang, W. Xu, H. Zhao, H. Kohlhammer, A. Rosenwald, P. Kluin, H.K. Muller-Hermelink, G. Ott, R.D. Gascoyne, J.M. Connors, L.M. Rimsza, E. Campo, E.S. Jaffe, J. Delabie, E.B. Smeland, M.D. Ogwang, S.J. Reynolds, R.I. Fisher, R.M. Braziel, R.R. Tubbs, J.R. Cook, D.D. Weisenburger, W.C. Chan, S. Pittaluga, W. Wilson, T.A. Waldmann, M. Rowe, S.M. Mbulaiteye, A.B. Rickinson, L.M. Staudt, Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics, Nature 490 (2012) 116–120.
[91] G.A. Calin, C.D. Dumitru, M. Shimizu, R. Bichi, S. Zupo, E. Noch, H. Aldler, S. Rattan, M. Keating, K. Rai, L. Rassenti, T. Kipps, M. Negrini, F. Bullrich, C.M. Croce, Frequent

deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 15524–15529.
[92] T.C. Chang, D. Yu, Y.S. Lee, E.A. Wentzel, D.E. Arking, K.M. West, C.V. Dang, A. Thomas-Tikhonenko, J.T. Mendell, Widespread microRNA repression by Myc contributes to tumorigenesis, Nat. Genet. 40 (2008) 43–50.
[93] X. Zhang, X. Zhao, W. Fiskus, J. Lin, T. Lwin, R. Rao, Y. Zhang, J.C. Chan, K. Fu, V.E. Marquez, S. Chen-Kiang, L.C. Moscinski, E. Seto, W.S. Dalton, K.L. Wright, E. Sotomayor, K. Bhalla, J. Tao, Coordinated silencing of MYC-mediated miR-29 by HDAC3 and EZH2 as a therapeutic target of histone modification in aggressive B-cell lymphomas, Cancer Cell 22 (2012) 506–523.
[94] X. Zhang, X. Chen, J. Lin, T. Lwin, G. Wright, L.C. Moscinski, W.S. Dalton, E. Seto, K. Wright, E. Sotomayor, J. Tao, Myc represses miR-15a/miR-16-1 expression through recruitment of HDAC3 in mantle cell and other non-Hodgkin B-cell lymphomas, Oncogene 31 (2012) 3002–3008.
[95] V.B. Sampson, N.H. Rong, J. Han, Q. Yang, V. Aris, P. Soteropoulos, N.J. Petrelli, S.P. Dunn, L.J. Krueger, MicroRNA let-7a down-regulates MYC and reverts MYC-induced growth in Burkitt lymphoma cells, Cancer Res. 67 (2007) 9762–9770.
[96] T.C. Chang, L.R. Zeitels, H.W. Hwang, R.R. Chivukula, E.A. Wentzel, M. Dews, J. Jung, P. Gao, C.V. Dang, M.A. Beer, A. Thomas-Tikhonenko, J.T. Mendell, Lin-28B transactivation is necessary for Myc-mediated let-7 repression and proliferation, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 3384–3389.
[97] T.V. Bui, J.T. Mendell, Myc: Maestro of MicroRNAs, Genes Cancer 1 (2010) 568–575.
[98] L. Xiong, W. Jiang, R. Zhou, C. Mao, Z. Guo, Identification and analysis of the regulatory network of Myc and microRNAs from high-throughput experimental data, Comput. Biol. Med. 43 (2013) 1252–1260.
[99] C.M. Eischen, J.D. Weber, M.F. Roussel, C.J. Sherr, J.L. Cleveland, Disruption of the ARF-Mdm2-p53 tumor suppressor pathway in Myc-induced lymphomagenesis, Genes Dev. 13 (1999) 2658–2669.
[100] M.T. Hemann, J.T. Zilfou, Z. Zhao, D.J. Burgess, G.J. Hannon, S.W. Lowe, Suppression of tumorigenesis by the p53 target PUMA, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 9333–9338.
[101] A. Villunger, E.M. Michalak, L. Coultas, F. Mullauer, G. Bock, M.J. Ausserlechner, J.M. Adams, A. Strasser, p53- and drug-induced apoptotic responses mediated by BH3-only proteins puma and noxa, Science (New York, N.Y.) 302 (2003) 1036–1038.
[102] E.M. Michalak, E.S. Jansen, L. Happo, M.S. Cragg, L. Tai, G.K. Smyth, A. Strasser, J.M. Adams, C.L. Scott, Puma and to a lesser extent Noxa are suppressors of Myc-induced lymphomagenesis, Cell Death Differ. 16 (2009) 684–696.
[103] C.M. Eischen, M.F. Roussel, S.J. Korsmeyer, J.L. Cleveland, Bax loss impairs Myc-induced apoptosis and circumvents the selection of p53 mutations during Myc-mediated lymphomagenesis, Mol. Cell. Biol. 21 (2001) 7653–7662.
[104] D.L. Vaux, S. Cory, J.M. Adams, Bcl-2 gene promotes haemopoietic cell survival and cooperates with c-myc to immortalize pre-B cells, Nature 335 (1988) 440–442.
[105] R.P. Bissonnette, F. Echeverri, A. Mahboubi, D.R. Green, Apoptotic cell death induced by c-myc is inhibited by bcl-2, Nature 359 (1992) 552–554.
[106] G. Gaidano, P. Ballerini, J.Z. Gong, G. Inghirami, A. Neri, E.W. Newcomb, I.T. Magrath, D.M. Knowles, R. Dalla-Favera, p53 mutations in human lymphoid malignancies: association with Burkitt lymphoma and chronic lymphocytic leukemia, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 5413–5417.
[107] K.G. Bhatia, M.I. Gutierrez, K. Huppi, D. Siwarski, I.T. Magrath, The pattern of p53 mutations in Burkitt's lymphoma differs from that of solid tumors, Cancer Res. 52 (1992) 4273–4276.
[108] K.D. Mason, C.J. Vandenberg, C.L. Scott, A.H. Wei, S. Cory, D.C. Huang, A.W. Roberts, In vivo efficacy of the Bcl-2 antagonist ABT-737 against aggressive Myc-driven lymphomas, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 17961–17966.
[109] M.F. van Delft, A.H. Wei, K.D. Mason, C.J. Vandenberg, L. Chen, P.E. Czabotar, S.N. Willis, C.L. Scott, C.L. Day, S. Cory, J.M. Adams, A.W. Roberts, D.C. Huang, The BH3 mimetic ABT-737 targets selective Bcl-2 proteins and efficiently induces apoptosis via Bak/Bax if Mcl-1 is neutralized, Cancer Cell 10 (2006) 389–399.
[110] G.L. Kelly, S. Grabow, S.P. Glaser, L. Fitzsimmons, B.J. Aubrey, T. Okamoto, L.J. Valente, M. Robati, L. Tai, W.D. Fairlie, E.F. Lee, M.S. Lindstrom, K.G. Wiman, D.C. Huang, P. Bouillet, M. Rowe, A.B. Rickinson, M.J. Herold, A. Strasser, Targeting of MCL-1 kills MYC-driven mouse and human lymphomas even when they bear mutations in p53, Genes Dev. 28 (2014) 58–70.
[111] L. Srinivasan, Y. Sasaki, D.P. Calado, B. Zhang, J.H. Paik, R.A. DePinho, J.L. Kutok, J.F. Kearney, K.L. Otipoby, K. Rajewsky, PI3 kinase signals BCR-dependent mature B cell survival, Cell 139 (2009) 573–586.
[112] J. Richter, M. Schlesner, S. Hoffmann, M. Kreuz, E. Leich, B. Burkhardt, M. Rosolowski, O. Ammerpohl, R. Wagener, S.H. Bernhart, D. Lenze, M. Szczepanowski, M. Paulsen, S. Lipinski, R.B. Russell, S. Adam-Klages, G. Apic, A. Claviez, D. Hasenclever, V. Hovestadt, N. Hornig, J.O. Korbel, D. Kube, D. Langenberger, C. Lawerenz, J. Lisfeld, K. Meyer, S. Picelli, J. Pischimarov, B. Radlwimmer, T. Rausch, M. Rohde, M. Schilhabel, R. Scholtysik, R. Spang, H. Trautmann, T. Zenz, A. Borkhardt, H.G. Drexler, P. Moller, R.A. MacLeod, C. Pott, S. Schreiber, L. Trumper, M. Loeffler, P.F. Stadler, P. Lichter, R. Eils, R. Kuppers, M. Hummel, W. Klapper, P. Rosenstiel, A. Rosenwald, B. Brors, R. Siebert, Recurrent mutation of the ID3 gene in Burkitt lymphoma identified by integrated genome, exome and transcriptome sequencing, Nat. Genet. 44 (2012) 1316–1320.
[113] M.H. Cato, S.K. Chintalapati, I.W. Yau, S.A. Omori, R.C. Rickert, Cyclin D3 is selectively required for proliferative expansion of germinal center B cells, Mol. Cell. Biol. 31 (2011) 127–137.
[114] J.U. Peled, J.J. Yu, J. Venkatesh, E. Bi, B.B. Ding, M. Krupski-Downs, R. Shaknovich, P. Sicinski, B. Diamond, M.D. Scharff, B.H. Ye, Requirement for cyclin D3 in germinal center formation and function, Cell Res. 20 (2010) 631–646.
[115] C.J. Fox, P.S. Hammerman, R.M. Cinalli, S.R. Master, L.A. Chodosh, C.B. Thompson, The serine/threonine kinase Pim-2 is a transcriptionally regulated apoptotic inhibitor, Genes Dev. 17 (2003) 1841–1854.
[116] L.P. Forshell, Y. Li, T.Z. Forshell, M. Rudelius, L. Nilsson, U. Keller, J. Nilsson, The direct Myc target Pim3 cooperates with other Pim kinases in supporting viability of Myc-induced B-cell lymphomas, Oncotarget 2 (2011) 448–460.
[117] S. Verbeek, M. van Lohuizen, M. van der Valk, J. Domen, G. Kraal, A. Berns, Mice bearing the E mu-myc and E mu-pim-1 transgenes develop pre-B-cell leukemia prenatally, Mol. Cell. Biol. 11 (1991) 1176–1179.
[118] Y.W. Lin, Z.M. Beharry, E.G. Hill, J.H. Song, W. Wang, Z. Xia, Z. Zhang, P.D. Aplan, J.C. Aster, C.D. Smith, A.S. Kraft, A small molecule inhibitor of Pim protein kinases blocks the growth of precursor T-cell lymphoblastic leukemia/lymphoma, Blood 115 (2010) 824–833.
[119] J.D. Allen, E. Verhoeven, J. Domen, M. van der Valk, A. Berns, Pim-2 transgene induces lymphoid tumors, exhibiting potent synergy with c-myc, Oncogene 15 (1997) 1133–1141.
[120] L. Soucek, J. Whitfield, C.P. Martins, A.J. Finch, D.J. Murphy, N.M. Sodir, A.N. Karnezis, L.B. Swigart, S. Nasi, G.I. Evan, Modelling Myc inhibition as a cancer therapy, Nature 455 (2008) 679–683.
[121] P.S. Choi, J. van Riggelen, A.J. Gentles, P. Bachireddy, K. Rakhra, S.J. Adam, S.K. Plevritis, D.W. Felsher, Lymphomas that recur after MYC suppression continue to exhibit oncogene addiction, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 17432–17437.
[122] M. Savino, D. Annibali, N. Carucci, E. Favuzzi, M.D. Cole, G.I. Evan, L. Soucek, S. Nasi, The action mechanism of the Myc inhibitor termed Omomyc may give clues on how to target Myc for cancer therapy, PLoS One 6 (2011) e22284.
[123] L. Soucek, M. Helmer-Citterich, A. Sacco, R. Jucker, G. Cesareni, S. Nasi, Design and properties of a Myc derivative that efficiently homodimerizes, Oncogene 17 (1998) 2463–2472.
[124] J. Guo, R.A. Parise, E. Joseph, M.J. Egorin, J.S. Lazo, E.V. Prochownik, J.L. Eiseman, Efficacy, pharmacokinetics, tisssue distribution, and metabolism of the Myc-Max disruptor, 10058–F4 [Z, E]-5-[4-ethylbenzylidine]-2-thioxothiazolidin-4-one, in mice, Cancer Chemother. Pharmacol. 63 (2009) 615–625.
[125] E.V. Prochownik, P.K. Vogt, Therapeutic targeting of Myc, Genes Cancer 1 (2010) 650–659.
[126] J.E. Delmore, G.C. Issa, M.E. Lemieux, P.B. Rahl, J. Shi, H.M. Jacobs, E. Kastritis, T. Gilpatrick, R.M. Paranal, J. Qi, M. Chesi, A.C. Schinzel, M.R. McKeown, T.P. Heffernan, C.R. Vakoc, P.L. Bergsagel, I.M. Ghobrial, P.G. Richardson, R.A. Young, W.C. Hahn, K.C. Anderson, A.L. Kung, J.E. Bradner, C.S. Mitsiades, BET bromodomain inhibition as a therapeutic strategy to target c-Myc, Cell 146 (2011) 904–917.
[127] C.J. Ott, N. Kopp, L. Bird, R.M. Paranal, J. Qi, T. Bowman, S.J. Rodig, A.L. Kung, J.E. Bradner, D.M. Weinstock, BET bromodomain inhibition targets both c-Myc and IL7R in high-risk acute lymphoblastic leukemia, Blood 120 (2012) 2843–2852.
[128] A.C. Belkina, G.V. Denis, BET domain co-regulators in obesity, inflammation and cancer, Nat. Rev. Cancer 12 (2012) 465–477.
[129] B. Chapuy, M.R. McKeown, C.Y. Lin, S. Monti, M.G. Roemer, J. Qi, P.B. Rahl, H.H. Sun, K.T. Yeda, J.G. Doench, E. Reichert, A.L. Kung, S.J. Rodig, R.A. Young, M.A. Shipp, J.E. Bradner, Discovery and characterization of super-enhancer-associated dependencies in diffuse large B cell lymphoma, Cancer Cell 24 (2013) 777–790.
[130] J. Loven, H.A. Hoke, C.Y. Lin, A. Lau, D.A. Orlando, C.R. Vakoc, J.E. Bradner, T.I. Lee, R.A. Young, Selective inhibition of tumor oncogenes by disruption of super-enhancers, Cell 153 (2013) 320–334.
[131] W.A. Whyte, D.A. Orlando, D. Hnisz, B.J. Abraham, C.Y. Lin, M.H. Kagey, P.B. Rahl, T.I. Lee, R.A. Young, Master transcription factors and mediator establish super-enhancers at key cell identity genes, Cell 153 (2013) 307–319.
[132] D. Hnisz, B.J. Abraham, T.I. Lee, A. Lau, V. Saint-Andre, A.A. Sigova, H.A. Hoke, R.A. Young, Super-enhancers in the control of cell identity and disease, Cell 155 (2013) 934–947.
[133] P. Filippakopoulos, J. Qi, S. Picaud, Y. Shen, W.B. Smith, O. Fedorov, E.M. Morse, T. Keates, T.T. Hickman, I. Felletar, M. Philpott, S. Munro, M.R. McKeown, Y. Wang, A.L. Christie, N. West, M.J. Cameron, B. Schwartz, T.D. Heightman, N. La Thangue, C.A. French, O. Wiest, A.L. Kung, S. Knapp, J.E. Bradner, Selective inhibition of BET bromodomains, Nature 468 (2010) 1067–1073.
[134] E. Nicodeme, K.L. Jeffrey, U. Schaefer, S. Beinke, S. Dewell, C.W. Chung, R. Chandwani, I. Marazzi, P. Wilson, H. Coste, J. White, J. Kirilovsky, C.M. Rice, J.M. Lora, R.K. Prinjha, K. Lee, A. Tarakhovsky, Suppression of inflammation by a synthetic histone mimic, Nature 468 (2010) 1119–1123.
[135] J. Zuber, J. Shi, E. Wang, A.R. Rappaport, H. Herrmann, E.A. Sison, D. Magoon, J. Qi, K. Blatt, M. Wunderlich, M.J. Taylor, C. Johns, A. Chicas, J.C. Mulloy, S.C. Kogan, P. Brown, P. Valent, J.E. Bradner, S.W. Lowe, C.R. Vakoc, RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia, Nature 478 (2011) 524–528.
[136] J.A. Mertz, A.R. Conery, B.M. Bryant, P. Sandy, S. Balasubramanian, D.A. Mele, L. Bergeron, R.J. Sims 3rd, Targeting MYC dependence in cancer by inhibiting BET bromodomains, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 16669–16674.
[137] M.A. Dawson, R.K. Prinjha, A. Dittmann, G. Giotopoulos, M. Bantscheff, W.I. Chan, S.C. Robson, C.W. Chung, C. Hopf, M.M. Savitski, C. Huthmacher, E. Gudgin, D. Lugo, S. Beinke, T.D. Chapman, E.J. Roberts, P.E. Soden, K.R. Auger, O. Mirguet, K. Doehner, R. Delwel, A.K. Burnett, P. Jeffrey, G. Drewes, K. Lee, B.J. Huntly, T. Kouzarides, Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia, Nature 478 (2011) 529–533.
[138] L.S. Chen, S. Redkar, D. Bearss, W.G. Wierda, V. Gandhi, Pim kinase inhibitor, SGI-1776, induces apoptosis in chronic lymphocytic leukemia cells, Blood 114 (2009) 4150–4157.
[139] L.S. Chen, S. Redkar, P. Taverna, J.E. Cortes, V. Gandhi, Mechanisms of cytotoxicity to Pim kinase inhibitor, SGI-1776, in acute myeloid leukemia, Blood 118 (2011) 693–702.
[140] H. Mikkers, M. Nawijn, J. Allen, C. Brouwers, E. Verhoeven, J. Jonkers, A. Berns, Mice deficient for all PIM kinases display reduced body size and impaired responses to hematopoietic growth factors, Mol. Cell. Biol. 24 (2004) 6104–6115.

[141] M. Nguyen, R.C. Marcellus, A. Roulston, M. Watson, L. Serfass, S.R. Murthy Madiraju, D. Goulet, J. Viallet, L. Belec, X. Billot, S. Acoca, E. Purisima, A. Wiegmans, L. Cluse, R.W. Johnstone, P. Beauparlant, G.C. Shore, Small molecule obatoclax (GX15-070) antagonizes MCL-1 and overcomes MCL-1-mediated resistance to apoptosis, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 19512–19517.
[142] L.C. Spender, G.J. Inman, Phosphoinositide 3-kinase/AKT/mTORC1/2 signaling determines sensitivity of Burkitt's lymphoma cells to BH3 mimetics, Mol. Cancer Res. 10 (2012) 347–359.
[143] D.W. Fry, P.J. Harvey, P.R. Keller, W.L. Elliott, M. Meade, E. Trachet, M. Albassam, X. Zheng, W.R. Leopold, N.K. Pryer, P.L. Toogood, Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts, Mol. Cancer Ther. 3 (2004) 1427–1438.
[144] J.W. Friedberg, D. Mahadevan, E. Cebula, D. Persky, I. Lossos, A.B. Agarwal, J. Jung, R. Burack, X. Zhou, E.J. Leonard, H. Fingert, H. Danaee, S.H. Bernstein, Phase II study of alisertib, a selective aurora a kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphomas, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 32 (2014) 44–50.
[145] A. Le, C.R. Cooper, A.M. Gouw, R. Dinavahi, A. Maitra, L.M. Deck, R.E. Royer, D.L. Vander Jagt, G.L. Semenza, C.V. Dang, Inhibition of lactate dehydrogenase A induces oxidative stress and inhibits tumor progression, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 2037–2042.
[146] M.L. Wahl, J.A. Owen, R. Burd, R.A. Herlands, S.S. Nogami, U. Rodeck, D. Berd, D.B. Leeper, C.S. Owen, Regulation of intracellular pH in human melanoma: potential therapeutic implications, Mol. Cancer Ther. 1 (2002) 617–628.
[147] S. Bonnet, S.L. Archer, J. Allalunis-Turner, A. Haromy, C. Beaulieu, R. Thompson, C.T. Lee, G.D. Lopaschuk, L. Puttagunta, G. Harry, K. Hashimoto, C.J. Porter, M.A. Andrade, B. Thebaud, E.D. Michelakis, A mitochondria-K + channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth, Cancer Cell 11 (2007) 37–51.
[148] S. Fujiwara, Y. Kawano, H. Yuki, Y. Okuno, K. Nosaka, H. Mitsuya, H. Hata, PDK1 inhibition is a novel therapeutic target in multiple myeloma, Br. J. Cancer 108 (2013) 170–178.
[149] G. Qing, B. Li, A. Vu, N. Skuli, Z.E. Walton, X. Liu, P.A. Mayes, D.R. Wise, C.B. Thompson, J.M. Maris, M.D. Hogarty, M.C. Simon, ATF4 regulates MYC-mediated neuroblastoma cell death upon glutamine deprivation, Cancer Cell 22 (2012) 631–644.
[150] N. Niitsu, M. Okamoto, I. Miura, M. Hirano, Clinical features and prognosis of de novo diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC translocations, Leuk. Off. J. Leuk. Soc. Am. Leuk. Res. Fund UK 23 (2009) 777–783.
[151] P. Bertrand, C. Bastard, C. Maingonnat, F. Jardin, C. Maisonneuve, M.N. Courel, P. Ruminy, J.M. Picquenot, H. Tilly, Mapping of MYC breakpoints in 8q24 rearrangements involving non-immunoglobulin partners in B-cell lymphomas, Leuk. Off. J. Leuk. Soc. Am. Leuk. Res. Fund UK 21 (2007) 515–523.
[152] H. Avet-Loiseau, F. Gerson, F. Magrangeas, S. Minvielle, J.L. Harousseau, R. Bataille, Rearrangements of the c-myc oncogene are present in 15% of primary human multiple myeloma tumors, Blood 98 (2001) 3082–3086.
[153] Y. Shou, M.L. Martelli, A. Gabrea, Y. Qi, L.A. Brents, A. Roschke, G. Dewald, I.R. Kirsch, P.L. Bergsagel, W.M. Kuehl, Diverse karyotypic abnormalities of the c-myc locus associated with c-myc dysregulation and tumor progression in multiple myeloma, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 228–233.
[154] S. Faderl, S. O'Brien, C.H. Pui, W. Stock, M. Wetzler, D. Hoelzer, H.M. Kantarjian, Adult acute lymphoblastic leukemia: concepts and strategies, Cancer 116 (2010) 1165–1176.
[155] D. De Jong, B.M. Voetdijk, G.C. Beverstock, G.J. van Ommen, R. Willemze, P.M. Kluin, Activation of the c-myc oncogene in a precursor-B-cell blast crisis of follicular lymphoma, presenting as composite lymphoma, N. Engl. J. Med. 318 (1988) 1373–1378.
[156] K.H. Young, Q. Xie, G. Zhou, J.C. Eickhoff, W.G. Sanger, P. Aoun, W.C. Chan, Transformation of follicular lymphoma to precursor B-cell lymphoblastic lymphoma with c-myc gene rearrangement as a critical event, Am. J. Clin. Pathol. 129 (2008) 157–166.
[157] G.W. Slack, R.D. Gascoyne, MYC and aggressive B-cell lymphomas, Adv. Anat. Pathol. 18 (2011) 219–228.
[158] R. Setoodeh, S. Schwartz, P. Papenhausen, L. Zhang, E.M. Sagatys, L.C. Moscinski, H. Shao, Double-hit mantle cell lymphoma with MYC gene rearrangement or amplification: a report of four cases and review of the literature, Int. J. Clin. Exp. Pathol. 6 (2013) 155–167.
[159] N. Put, K. Van Roosbroeck, P. Konings, P. Meeus, C. Brusselmans, K. Rack, C. Gervais, F. Nguyen-Khac, E. Chapiro, I. Radford-Weiss, S. Struski, N. Dastugue, N. Gachard, C. Lefebvre, C. Barin, V. Eclache, S. Fert-Ferrer, S. Laibe, M.J. Mozziconacci, B. Quilichini, H.A. Poirel, I. Wlodarska, A. Hagemeijer, Y. Moreau, P. Vandenberghe, L. Michaux, Chronic lymphocytic leukemia and prolymphocytic leukemia with MYC translocations: a subgroup with an aggressive disease course, Ann. Hematol. 91 (2012) 863–873.