Clin Transl Oncol (2013) 15:87–94
DOI 10.1007/s12094-012-0926-8

MYC oncogene in myeloid neoplasias

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Received: 6 July 2012 / Accepted: 24 July 2012 / Published online: 22 August 2012

Abstract MYC is a transcription factor that regulates many critical genes for cell proliferation, differentiation, and biomass accumulation. MYC is one of the most prevalent oncogenes found to be altered in human cancer, being deregulated in about 50 % of tumors. Although MYC deregulation has been more frequently associated to lymphoma and lymphoblastic leukemia than to myeloid malignancies, a body of evidence has been gathered showing that MYC plays a relevant role in malignancies derived from the myeloid compartment. The myeloid leukemogenic activity of MYC has been demonstrated in different murine models. Not surprisingly, MYC has been found to be amplified or/and deregulated in the three major types of myeloid neoplasms: acute myeloid leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms, including chronic myeloid leukemia. Here, we review the recent literature describing the involvement of MYC in myeloid tumors.

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Keywords MYC · Myeloid neoplasia · Acute myeloid leukemia · Chronic myeloid leukemia · Myelodysplastic syndromes

Myelopoiesis and MYC impact on myeloid cell proliferation and differentiation

Hematopoietic stem cells differentiate along two major lineages. The lymphoid lineages give rise to B- and T-lymphocytes, as well as natural killer cells. The myeloid lineage is much more complex, with at least six major differentiated circulating cells (erythrocytes, monocyte/macrophages, eosinophils, neutrophils, basophils, and megakaryocyte/platelets) each of them very different from the other cell types in its function in the organism, its number in peripheral blood, and its morphology and gene expression profile [1–3]. Myeloid lineage commitment relies on timely activation of appropriate transcription factors and silencing of others, which is the result from a network of extracellular signals [4, 5].

MYC is a transcription factor of the helix-loop-helix-leucine zipper family. MYC forms dimers with MAX protein and binds to E-box sequences in the regulatory regions of around one thousand target genes (Fig. 1a) [6]. MYC is involved in a number of fundamental functions for the cell biology, such as control of proliferation and differentiation, energy production, cell size, and many others (Fig. 1b) [7–9]. Not surprisingly, deregulation of MYC activities contributes to the tumor phenotype. MYC is one of the most prevalent oncogenes in human cancer, and particularly in hematopoietic neoplasias [10, 11]. In fact, in human cancer, MYC deregulation was first observed in Burkitt lymphoma, as well as in chemically induced murine plasmacytomas [12]. Virtually all cases of these

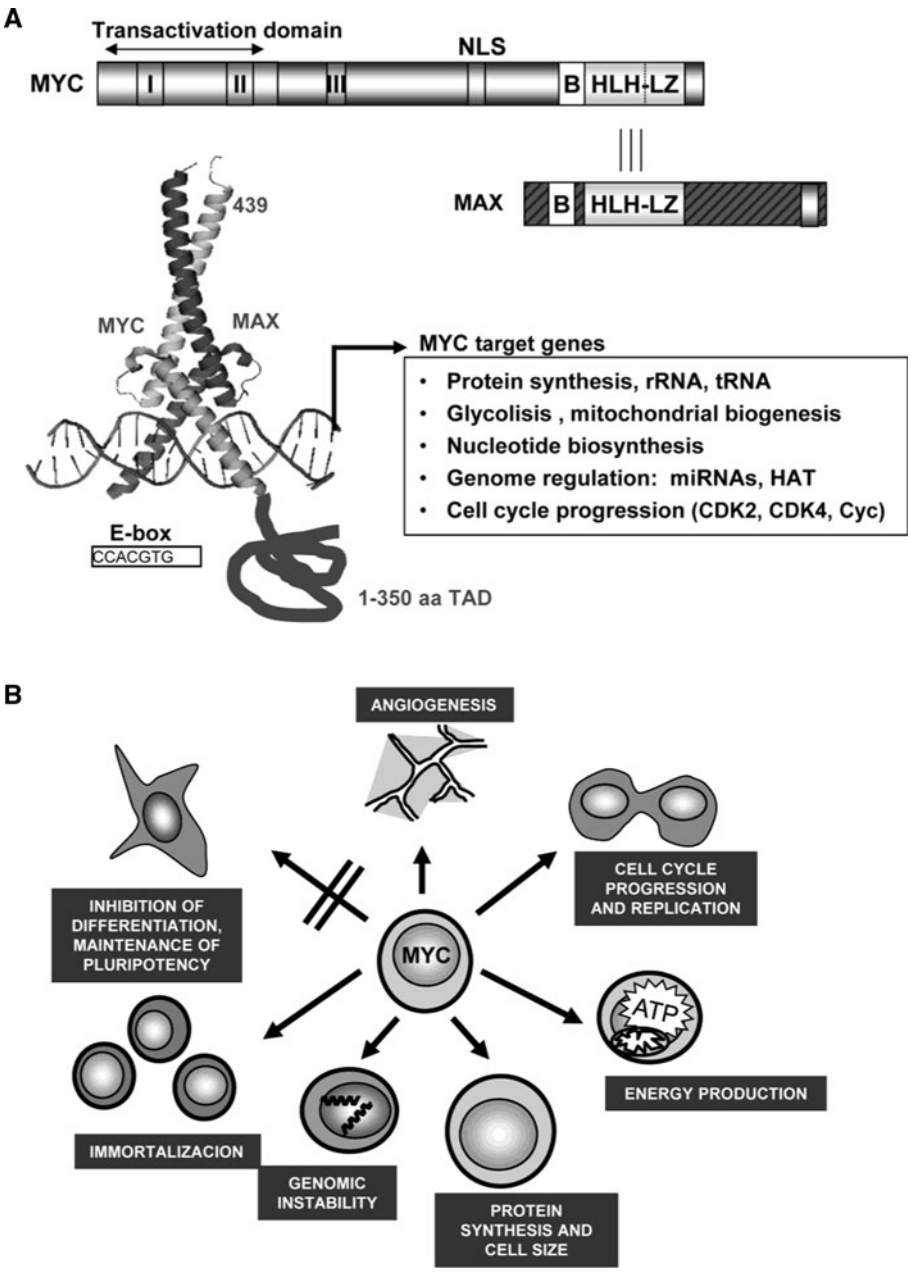

Fig. 1 MYC structure and functions. **a** Scheme showing the main features of MYC transcription factor: the N-terminal transactivation domain (TAD), conserved MYC box-I, II, and III, nuclear localization signal (NLS), and the basic-helix-loop-helix-leuzine zipper (B-HLH-LZ) DNA binding and dimerization domain. Heterodimers MYC-MAX bind E-box sequences at the regulatory regions of its target genes (the most representative indicated in the *square*). **b** MYC is involved in many cellular functions through the regulation (activation or repression) of its target genes. MYC favors the cell cycle progression by activating cyclin-dependent kinases (CDKs) and repressing CDK inhibitors; MYC regulates metabolic enzymes involved in the ATP production; MYC has a role in protein synthesis and cell size through the control of ribosomal genes among others; MYC induces genomic instability and cell immortalization; the inhibition of cell differentiation, maintenance of pluripotency, and induction of angiogenesis are important MYC functions. Elevated MYC levels (by gene amplification, chromosomal translocation, overexpression, and protein stabilization) deregulate such functions, contributing to tumorigenesis

lymphoma show a translocation affecting the MYC locus [13]. From then on, MYC translocations have been found in a significant fraction of high-grade lymphomas and multiple myeloma, and MYC overexpression has also been reported in numerous types of lymphoma and lymphoblastic leukemia [14].

In contrast to lymphoid tumors, MYC involvement in myeloid cancer has received much less attention. Nonetheless, MYC oncogene was first discovered as the oncogene carried by retrovirus that induced a myeloid neoplasm in chicken, i.e., myelocytomatosis, and MYC was named after this tumor [15]. Moreover, the inhibition of myeloid cell differentiation was one of the first biological effects described for MYC (reviewed in Ref. [9]). In 1986, three reports showed that MYC blocked the chemically induced erythroid differentiation of Friend murine erythroleukemia (MEL) cells [16–18]. We also showed that MYC inhibited the erythroid differentiation of human myeloid cells such as K562 derived from chronic myeloid leukemia (CML) [19], and found that MYC blocks erythroid differentiation in genetically-defined models where erythroid differentiation is induced by $p27^{KIP1}$ [20]. In this model, MYC impairs the up-regulation of many erythroid-specific genes, as well as that of transcription factors that determine erythroid lineage differentiation (including GATA1 and NFE2) but, strikingly, it does not reverse the proliferation

arrest and the repression of CDK activity mediated by $p27^{KIP1}$. In a complementary approach, using the leukemia K562 and U937 cells, it has been shown that MYC is not down-regulated when cells are growth-arrested but not differentiated [21, 22]. Enforced MYC expression also blocks the monocytic differentiation of the AML-derived cell line U937 [23]. The fact that MYC can block differentiation of myeloid leukemia cells models in culture is consistent with its involvement in myeloid leukemia. However, MYC activity is not universally linked to differentiation inhibition of myeloid cells, as MYC enhances the retinoic acid-induced differentiation of a promyelocytic leukemia cell line (NB4) [24].

MYC roles in the determination of myeloid lineages in vivo

The results described above are consistent with the in vivo observed data. The effects of MYC deletion in the myeloid compartment have been recently reported in the MYC conditional knock-out mice. $Myc^{-/-}$ mice show significant thrombocytosis, severe anemia, and grossly decreased neutrophil/monocyte numbers [25]. Thus MYC induces opposite effects in the differentiation of megakaryocytic versus monocyte and erythroid lineages. Moreover, these effects of MYC deletion in vivo on hematopoietic lineages correlates well with MYC expression in mouse hematopoietic cells: cells expressing higher levels of MYC such as granulocyte/monocyte precursors, common lymphocyte progenitors, and erythrocytic blasts are significantly reduced while cells expressing lower MYC levels (hematopoietic stem cells (HSC), megakaryocyte/erythroid precursors, and megakaryocytes) are less affected or are increased in number [25].

Megakaryocytes from $Myc^{-/-}$ mice are significantly smaller in size and are lower in ploidy than those of control mice; as a result, fewer platelets are produced by each megakaryocyte. However, due to the increase in megakaryocytic number, a significant increase in platelet number was observed in $Myc^{-/-}$ mice. The involvement of MYC in megakaryocytic differentiation is confirmed in transgenic mice with MYC overexpression in the megakaryocytic lineage, where a *Myc* transgene is under the control of the platelet factor-4 promoter. These mice show an increase in low-ploidy megakaryocytes due to enhanced proliferation and survival, along with the blocking of differentiation [26].

In conclusion, MYC plays a pivotal role in regulating the normal hematopoiesis, and thus, it is not surprising that MYC is frequently deregulated in human leukemia and lymphoma. Such deregulation would destroy this balance and transform hematopoietic cells by stimulating proliferation and blocking terminal differentiation.

In vivo models for MYC-induced myeloid leukemia: engraftment of retrovirally mediated expression of MYC in hematopoietic precursors

Several reports illustrate the leukemogenic effects of MYC in hematopoietic cells after the enforced expression in murine hematopoietic precursors via retroviral infection, although the induced neoplasia varies depending on the virus and the cells type targeted by the virus. Unfractionated bone marrow cells retrovirally transduced with *Myc,* using different vectors and experimental settings, resulted in development of acute myeloid leukemia (AML) [27–29]. In one study, the MYC-transduced fetal liver cells transduced with another MYC vector induced a long-latency lymphoma [30].

The infection of bone marrow progenitors in a $p53^{-/-}$ background also resulted in lymphoma [31]. Interestingly, upon culturing in vitro, cells derived from these lymphomas underwent myeloid differentiation, but then switched from myeloid to lymphoid lineage and induced B cell lymphomas when returning to in vivo conditions [32]. In another study, mice bone marrow cells transduced with another member of the MYC family, MYCN (also called N-Myc), developed monoclonal and transplantable AML [33]. In a parallel report, it was shown that when the bone marrow from lethally irradiated cells was repopulated with bone marrow cells expressing *Myc*, the mice developed an AML-like disease [29]. In this model, the co-expression of several antiapoptotic genes of the BCL2 family accelerated leukemogenesis but did not change the myeloid phenotype of the leukemia [29]. In conclusion, these experimental models indicate that high MYC levels switch normal hematopoiesis into myeloid leukemia. The analysis of the AML induced in some of these models showed high expression of the antiapoptotic genes of the BCL2 family including the MCL1 gene. Moreover, MCL1 haploinsufficiency abrogated AML development in this model [28]. The results suggest that abrogation of apoptosis in MYC-targeted cells is probably necessary for the development of an aggressive AML. This has been recently confirmed in another report, in which retroviral transduction of MYC in purified (Lin^-) murine HSC results in the development of both myeloid and T-lymphoid tumors within 2 months after transplantation. Interestingly, co-expression of MYC with BCLXL or BCL2 resulted in almost immediate development of AML-like disease, but not lymphoma (at the expense of other hematopoietic lineages) [34].

In vivo models for MYC-induced myeloid leukemia: transgenic mice developing myeloid neoplasia

Although most of the available literature on murine models of MYC-induced tumors is focused on MYC-induced

lymphoma, there are also transgenic models that demonstrate the carcinogenic potential of MYC in the myeloid compartment. Mice carrying the human MYC proto-oncogene under the control of the murine GATA-1 promoter (an erythroid-specific gene) developed an early onset erythroleukemia [35]. Several transgenic mice lines have been generated carrying the MYC gene under the control of the Vav promoter (which is active in all hematopoietic cells lineages and hematopoietic precursors) showing different MYC expression levels [36]. Interestingly, the tumor lineage varied with the different MYC expression levels achieved in the transgenic mice. For instance, aggressive T-cell lymphomas were the predominant tumor arising in transgenic mice lines showing the highest MYC expression [36]. In contrast, most tumors in the mouse lines expressing lower MYC levels were late-onset monocytic tumors [37]. It is noteworthy that just a two-fold decrease in MYC levels switched the phenotype from T-cell tumors to monocytic tumors. Thus, relatively low MYC levels can transform monocyte-macrophages but are insufficient to transform T-lymphocytes [37]. These data and other gathered in the literature strongly suggest that relatively small increases in MYC are sufficient to promote leukemia.

MYC in human myeloproliferative neoplasms

Consistent with the data gathered in animal models (see above), MYC deregulation has been found in human myeloid neoplasias. Three major groups of clonal myeloid diseases have been described: acute myeloid leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms [38]. Myeloproliferative neoplasms (MPN) are characterized by an enhanced proliferation of one or more of myeloid, erythroid, or megakaryocytic lineages. Chronic myeloid leukemia (CML) affects annually 1–2 cases per 100,000 individuals. CML is a proliferative clonal disorder of hematopoietic stem cells that results primarily in the expansion of mature myeloid cells that retains a capacity for differentiation. Untreated CML progress from the initial stage, termed chronic phase, to a blastic crisis phase which is similar to acute leukemia. Other frequent MPNs are essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF).

The Philadelphia chromosome and the resulting fusion Bcr-Abl oncogene is the universal molecular marker of CML and has a central role in the disease etiology [39]. Bcr-Abl up-regulates MYC expression [40, 41] and MYC cooperates with Bcr-Abl in transformation [42–44]. Moreover, Bcr-Abl provokes the phosphorylation of MYC in Ser-62. This phosphorylation renders a more stable MYC protein. A proteomic analysis revealed that MYC-Ser62 was largely dephosphorylated after dasatinib treatment [45]. This result suggests that these kinase inhibitors would reduce the levels of MYC protein in the leukemic cell.

Studies performed with a small number of cases, showed that *MYC* mRNA levels are elevated in CML-blastic crisis [46, 47] and in chronic phase CML versus healthy bone marrow samples [48, 49]. We have recently observed the up-regulation of MYC expression during CML progression [50]. Moreover, high levels of MYC along the disease correlate with poorer response to imatinib, and higher MYC mRNA levels at diagnosis tend to correlate with a worse response to imatinib [50]. Essentially the same results have been recently reported in a smaller cohort of CML patients, showing that MYC protein is elevated at diagnosis in patients destined to progress to blastic crisis [51]. It is also of note that trisomy 8 and gain at 8q24 (where MYC maps) are among the most frequent cytogenetic alterations in CML [52, 53], although their correlation with MYC expression is yet unknown.

It has been recently shown that at the time of diagnosis of CML, patients who will later progress to blast crisis have significantly higher levels of CIP2A protein (cancerous inhibitor of PP2A) [51]. CIP2A inhibits PP2A-mediated dephosphorylation of MYC at Ser-62, as pSer62-MYC is stabilized against degradation [54]. Although this should be confirmed in bigger cohorts of patients, these results indicate that CML progression is not only a consequence of elevated mRNA levels but also of MYC protein stabilization [51].

Misregulation of the activity of a specific group of ATP-binding cassette transporters (ABC) is responsible for reducing the intracellular concentration of drugs in leukemic cells. $CD34^{+}$ hematopoietic cell precursors of CML patients overexpress ABC transporters, and this overexpression is, at least in part, due to MYC, as *ABC* is a direct target of MYC [55]. This MYC activity could also contribute to CML transformation.

Why MYC should be deregulated during the CML progression? CML progression to blastic crisis is associated to cell survival, genomic instability, and differentiation arrest [39, 56]. We have shown that enforced MYC expression in CML-derived cells as K562, results in aberrant DNA synthesis under imatinib stress [50] and blocks imatinib-mediated differentiation [57], suggesting that MYC may contribute to CML transformation acting at those two levels (Fig. 2).

MYC mRNA is overexpressed in bone marrow cells from ET [58]. On the contrary, MYC overexpression is not found in the PV [58]. This is striking as more than 95 % of PV patients carry an activating mutation in the tyrosine kinase JAK2, and JAK2 has been reported to induce MYC expression in cell lines [40, 59]. Clearly, an analysis of STAT activation and the transcription factors phosphorylated by JAKs, is lacking in PV, making it difficult to obtain the interpretation of these results.

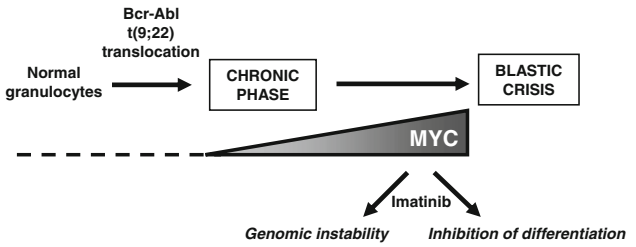

Fig. 2 MYC is overexpressed in chronic myeloid leukemia at diagnosis, and in blastic crisis. In CML-derived cells (K562 cell line) treated with imatinib, MYC induces genetic instability [50] and block of erythroid differentiation [57]

MYC in human myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)

Acute myeloid leukemia (AML) is characterized by the proliferation and accumulation of immature hematopoietic cells in the bone marrow and blood. AML is a heterogeneous group of neoplasms affecting the myeloid lineage. Altogether, their incidence worldwide is about 2–3 cases in 100,000 individuals per year, and is reported to be the highest in Australia, Western Europe, and United States. The former FAB (French-American-British) classification system of AML (M0 to M7 subtypes, attending to the differentiation type and stage) has been superseded by the World Health Organization (WHO) classification, that identifies 15 diseases characterized by clinical presentation and recurrent chromosomal aberrations [38]. Understandably, most molecular studies to date are carried out with a relatively small number of cases of each myeloid disease or do not make distinctions between the different entities. Therefore, the information on *MYC* expression in myeloid leukemia actually refers to a range of related diseases, and therefore its involvement in a particular myeloid neoplasm has not been properly addressed.

MYC amplification and overexpression have been found in AML [62] (Table 1). The overexpression of MYC mRNA in bone marrow and peripheral blood in sporadic AML cases patients (as compared with normal bone marrow) was observed early on [60, 61]. Subsequent studies bases on microarray hybridizations, and RT-qPCR analysis confirmed this finding and showed that not only MYC but also MYCN is overexpressed in AML patients [33]. These data are in agreement with the observation that MYC is up-regulated in radiation-induced AML in mice [62]. MYC expression also appeared elevated in a microarray-based study in 5 AML samples, and was validated by RT-qPCR [63]. In contrast, MYC has not been detected as a major overexpressed gene in other microarray-based studies on AML samples [64–66]. However, it must be noted, first, that microarray-based studies are done at the mRNA level, and thus changes in MYC protein level are not evaluated. Second, if MYC up-regulation is moderate (e.g., two-fold with respect to controls), it might be filtered out by the statistical analysis of microarray data. It should be mentioned, however, that a two-fold expression change of MYC may be relevant. For example, as noted above, transgenic mice lines with low MYC expression in the hematopoietic precursors develop myeloid leukemia; whereas, high MYC expression results in T cell lymphomas [37]. Also, a mere two-fold change means a major difference for MYC-dependent transformation of fibroblasts and mouse embryonic stem cells [67, 68] as well as in transgenic animals, where MYC dosage can be modulated [69]. This finding reveals that the impact of MYC in human leukemia is difficult to evaluate in the clinical setting, as two-fold increase in gene expression is usually not considered as significant when measuring mRNA expression in the clinical laboratories; whereas, as commented above, it could mean a difference in cell transformation. Finally, the great diversity of AML commented above makes the analysis of homogeneous sample cohorts difficult.

The mechanisms that lead to MYC overexpression in these cases are essentially unknown. Recurrent translocations in AML generate fusion proteins that are leukemogenic transcription factors, [38] and at least three of these (RUNX1-ETO, PML-RARα, and PLZF-RARα) induce MYC expression. Thus, MYC could be a downstream target of these oncogenes [70, 71]. On the other side, MYC might be mediating the effects of some of these oncogenic translocation products. For example, it has been shown that MYC mediates the block in granulocytic differentiation brought about by MLL-ENL [72].

Cytogenetic hallmarks of gene amplification in tumors are double minute (dmin) chromosomes and homogeneously staining regions (hsr). In contrast to other tumors, both double minute chromosomes and homogeneously staining regions containing amplified regions are rare in AML. Although MYC amplification in AML is infrequent (less than 1 % of all cytogenetically abnormal leukemias, http://cgap.nci.nih.gov/Chromosomes/Mitelman), hsr and dmin including the region of 8q24 where MYC maps have been consistently described in AML and 8q24 is one of the most common amplified regions in dmin [73–82]. It has been suggested that a high MYC gene copy number does not necessarily result in higher MYC expression [79, 83]. However, recent reports show that MYC amplification is associated with higher MYC expression, with disease progression and poor prognosis [75]. Also, $CD34^{+}$ cells from MDS patients with trisomy 8 showed up-regulation of MYC mRNA [84]. This situation is in agreement with the correlation between MYC amplification and expression observed in lymphoma [85].

Table 1 Summary of MYC alterations in myeloid malignancies

Leukemia	*MYC* deregulation	References
Chronic myeloid leukemia (CML)	MYC mRNA overexpression over healthy cells	[48, 49]
	High MYC mRNA and protein at diagnosis correlated with poor response to imatinib	[50]
	MYC protein elevated at diagnosis associated to progression. Altered MYC phosphorylation	[51]
Essential thrombocythemia (ET)	MYC mRNA overexpression	[58]
MDS	MYC mRNA up-regulation by microarray or RT-PCR	[84]
		[86]
	MYC amplification (in dmin and hsr)	[77, 78, 81, 84]
Acute myeloid leukemia (AML)	MYC amplification (in dmin)	[73–82]
	MYC mRNA overexpression by microarray analysis	[63]
AML (w/o translocations)	MYC mRNA overexpression by microarray (20 %)	[98]
AML (pediatric)	MYCN overexpression (24–40 %)	[33, 65]
AML (therapy-related)	MYC mRNA overexpression	[99]

The myelodysplastic syndromes (MDS) are also a heterogeneous group of clonal hematologic disorders characterized by both an aberrant differentiation process with morphologic evidence of marrow dysplasia in one or more of the three major myeloid cell types and an increased ineffective proliferation of the myeloid precursors in bone marrow, leading to cytopenia(s) and to an enhanced risk of transformation to an AML. Gene expression profiles of $CD34^+$ cells from MDS patients showed MYC as one of the most up-regulated genes in these patients [86]. Many patients with MDS, especially those with increased myeloblasts counts and adverse cytogenetic prognostic markers, will develop AML. MYC amplification has been reported with low frequencies in MDS [77, 78, 81, 84] (Table 1) but its prognostic impact is uncertain.

MYC as a pharmacological target in leukemia

As most transcription factors, MYC is not an easy druggable target. However, using dominant negative forms (OmoMyc), it has been shown that in vivo OmoMyc expression abolishes the MYC-mediated skin carcinogenesis in animal models [87]. Moreover, it has been shown that MYC blocks the K-Ras and T-antigen-dependent carcinogenesis in lung and pancreas, respectively [88–90]. This result suggests that MYC inhibition would be a sensible antitumor approach even for tumors that show no MYC deregulation. Several small molecules have been described as MYC inhibitors, although none of them are in clinical use at the moment. Most of them impair the MYC-MAX interaction, thus inhibiting the transcriptional activity of MYC [11]. This has the caveat that some of the MYC activities such as DNA replication, RNA pol II elongation, or CAP addition do not depend on the DNA binding activity of MYC [91, 92]. On the other hand, MYC requires other proteins for transformation, which may not be essential in normal cell physiology. Thus, a number of secondary targets capable of synthetic lethal interaction with MYC have been described, and thus proposed as putative pharmacological targets for MYC-driven tumors. This is the case of proteins as WRN [93], aurora kinase [94], CHK1 kinase [95] or CSKN1e kinase [96]. A different and recent approach is to block MYC expression by impairing BET bromodomain protein, a strategy shown to be effective in AML [97]. In summary, in vitro and in vivo models demonstrate a critical role of MYC in normal and malignant myelopoiesis. Therefore, the pharmacological targeting of MYC in myeloid leukemias is nowadays a challenge.

Acknowledgments This work, in the laboratory of the authors, was provided by grants SAF11-23796 and ISCIII-RETIC RD06/0020/0017 to JL, and FIS 11/00397 to MDD.

Conflict of interest The authors declare that they have no conflict of interest regarding the publication of this manuscript.

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