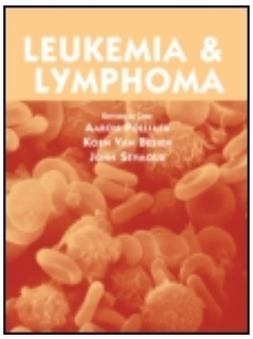

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

MYC addiction in chronic lymphocytic leukemia

Davide Rossi

To cite this article: Davide Rossi (2013) MYC addiction in chronic lymphocytic leukemia, Leukemia & Lymphoma, 54:5, 905-906, DOI: 10.3109/10428194.2012.755179

To link to this article: https://doi.org/10.3109/10428194.2012.755179

Leukemia & Lymphoma, May 2013; 54(5): 905–906

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2012.755179

informa
healthcare

COMMENTARY

MYC addiction in chronic lymphocytic leukemia

Davide Rossi

Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy

MYC is a transcription factor that lies at the crossroads of cell cycle and cell growth by acting downstream of many ligand–membrane receptor complexes and signal transduction pathways [1]. *MYC* is also a proto-oncogene that contributes to the genesis of many human cancers. The oncogenic activity of *MYC* begins when its normal transcriptional regulation is disrupted by abnormal microenvironmental interactions or gene lesions, which then lead to abnormally increased levels of intracellular MYC protein. Overexpression of *MYC* promotes tumorigenesis by activating the transcription of target genes that drive cell proliferation and growth [1].

Among B-cell tumors, *MYC* has been historically implicated in the molecular pathogenesis of aggressive non-Hodgkin lymphomas [2]. However, there is increasing evidence that *MYC* has a critical albeit incompletely understood role also in chronic lymphocytic leukemia (CLL), including the observations that: (i) a regulatory region centromeric to *MYC* contains multiple single nucleotide polymorphisms (SNPs) that have been implicated by genome-wide association studies (GWAS) in susceptibility to CLL [3]; (ii) *MYC* is activated by the engagement of a number of CLL surface receptors that are known to be relevant for the leukemic clone, including the B-cell receptor, NOTCH and BAFF [4–6]; (iii) expression of *MYC* and its target genes is increased in high risk CLL and in tumor compartments containing proliferating CLL cells (i.e. the lymph node), and correlates with poor outcome [4,7]; and (iv) transgenic mice expressing *MYC* together with *BAFF* develop a CLL-like disease [4].

Functional studies have documented that *MYC* deregulation in CLL is part of a program of downstream events mainly driven by microenvironmental interactions [4–7]. However, in a fraction of CLL, the *MYC* gene may be activated in a microenvironment-independent fashion by somatic structural lesions, including translocations with immunoglobulin and non-immunoglobulin loci (~1% of newly presented cases), gain/amplification at 8q24 (~5% of newly presented cases) and point mutations (~1% of newly presented cases) [8–10]. *MYC* lesions are associated with progressive CLL and accumulate in the advanced phases of the disease. In addition, consistent with a more general role of *MYC* deregulation in driving the transformation from indolent to aggressive B-cell lymphoproliferation, *MYC* abnormalities are particularly enriched in ~30–40% of cases of Richter syndrome, which is the histological shift of CLL to diffuse large B-cell lymphoma [11].

MYC belongs to a transcription regulating network that also includes *MAX*, a cofactor required for DNA binding by the various members of this network, as well as a group of putative *MYC* antagonists, namely *MNT*, *MXD1-4* and *MGA* [12]. In physiological conditions, the MYC protein activates gene transcription through heterodimerization with MAX and then by binding to the E-box DNA recognition sequences in its target gene promoters. Conversely, heterodimers of MAX with MNT, MXD1-4 and MGA antagonize MYC-dependent gene expression regulation by transcriptional repression of the same E-box sequences. On these bases, the MYC oncoprotein transforming ability depends also on the balance between the MYC–MAX and MNT/MXD1-4/MGA–MAX complexes [12].

In CLL, this balance may be disrupted by genetic lesions targeting *MYC* antagonists. Indeed, the *MYC* antagonist *MNT* is known to be recurrently affected by focal losses in a small proportion of CLL, as documented by high resolution SNP array [9]. In addition, three recent studies, including the report by De Paoli *et al*. in this issue of ***Leukemia and Lymphoma***, have independently shown that *MGA*, another MYC oncoprotein antagonist, is targeted by focal and recurrent gene deletions or truncating point mutations in a fraction of patients with CLL [9,13,14]. Though the clinical impact of these lesions needs to be formally defined in this leukemia, *MGA* abnormalities seem to be enriched in cases displaying high risk clinical features, namely fludarabine-refractoriness or transformation into Richter syndrome [14].

Overall, these findings suggest multiple functional and genetic mechanisms of *MYC* activation in CLL that, albeit occurring at a low frequency as single events, may account for a significant fraction of cases when integrated into a common pathway. The association between *MYC* functional or genetic deregulation and high risk clinical

Correspondence: Davide Rossi, Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy. Tel: +39 0321660698. Fax: +39 0321620421. E-mail: rossidav@med.unipmn.it

This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

features in CLL may suggest that *MYC* oncogene addiction is one of the paths leading to the development of a clinically aggressive phenotype in this leukemia and may represent a therapeutic target in cases that have transformed to Richter syndrome. Indeed, pharmacologic inhibition of the MYC oncoprotein is an attractive therapeutic strategy in tumors with deregulated or elevated MYC expression [1]. Among the strategies to target the MYC network, the BET bromodomain regulatory proteins recently emerged as potent inhibitors of MYC in different tumor types and have shown a significant preclinical activity in tumors known to depend on MYC addiction [15]. Will these compounds also have a role in CLL with deregulated *MYC*? The molecular data provided by De Paoli *et al.*, as well as other groups, represent a strong rationale for *MYC* targeting in CLL. However, the answer to this question can only be provided by the establishment of preclinical mouse models of high risk CLL and Richter syndrome with activated *MYC*. So, despite the promise, much remains to be done.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

References

[1] Dang CV. MYC on the path to cancer. Cell 2012;149:22–35.
[2] Salaverria I, Siebert R. The gray zone between Burkitt's lymphoma and diffuse large B-cell lymphoma from a genetics perspective. J Clin Oncol 2011;29:1835–1843.
[3] Crowther-Swanepoel D, Broderick P, Di Bernardo MC, et al. Common variants at 2q37.3, 8q24.21, 15q21.3 and 6q24.1 influence chronic lymphocytic leukemia risk. Nat Genet 2010;42:132–136.
[4] Zhang W, Kater AP, Widhopf GF 2nd, et al. B-cell activating factor and v-Myc myelocytomatosis viral oncogene homolog (c-Myc) influence progression of chronic lymphocytic leukemia. Proc Natl Acad Sci USA 2010;107:18956–18960.
[5] Fabbri G, Rasi S, Rossi D, et al. Analysis of the chronic lymphocytic leukemia coding genome: role of NOTCH1 mutational activation. J Exp Med 2011;208:1389–1401.
[6] Krysov S, Dias S, Paterson A, et al. Surface IgM stimulation induces MEK1/2-dependent MYC expression in chronic lymphocytic leukemia cells. Blood 2012;119:170–179.
[7] Herishanu Y, Pérez-Galán P, Liu D, et al. The lymph node microenvironment promotes B-cell receptor signaling, NF-kappaB activation, and tumor proliferation in chronic lymphocytic leukemia. Blood 2011;117:563–574.
[8] Huh YO, Lin KI, Vega F, et al. MYC translocation in chronic lymphocytic leukaemia is associated with increased prolymphocytes and a poor prognosis. Br J Haematol 2008;142:36–44.
[9] Edelmann J, Holzmann K, Miller F, et al. High-resolution genomic profiling of chronic lymphocytic leukemia reveals new recurrent genomic alterations. Blood 2012;120:4783–4794.
[10] Brown JR, Hanna M, Tesar B, et al. Integrative genomic analysis implicates gain of PIK3CA at 3q26 and MYC at 8q24 in chronic lymphocytic leukemia. Clin Cancer Res 2012;18:3791–3802.
[11] Rossi D, Spina V, Deambrogi C, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. Blood 2011;117:3391–3401.
[12] Cascón A, Robledo M. MAX and MYC: a heritable breakup. Cancer Res 2012;72:3119–3124.
[13] Puente XS, Pinyol M, Quesada V, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. Nature 2011;475:101–105.
[14] de Paoli L, Cerri M, Monti S, et al. *MGA*, a suppressor of *MYC*, is recurrently inactivated in high risk chronic lymphocytic leukemia. Leuk Lymphoma 2013;54;1087–1090.
[15] Delmore JE, Issa GC, Lemieux ME, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 2011;146: 904–917.