inside blood commentary

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LYMPHOID NEOPLASIA

Comment on Copie-Bergman et al, page 2466

MYC in DLBCL: partners matter

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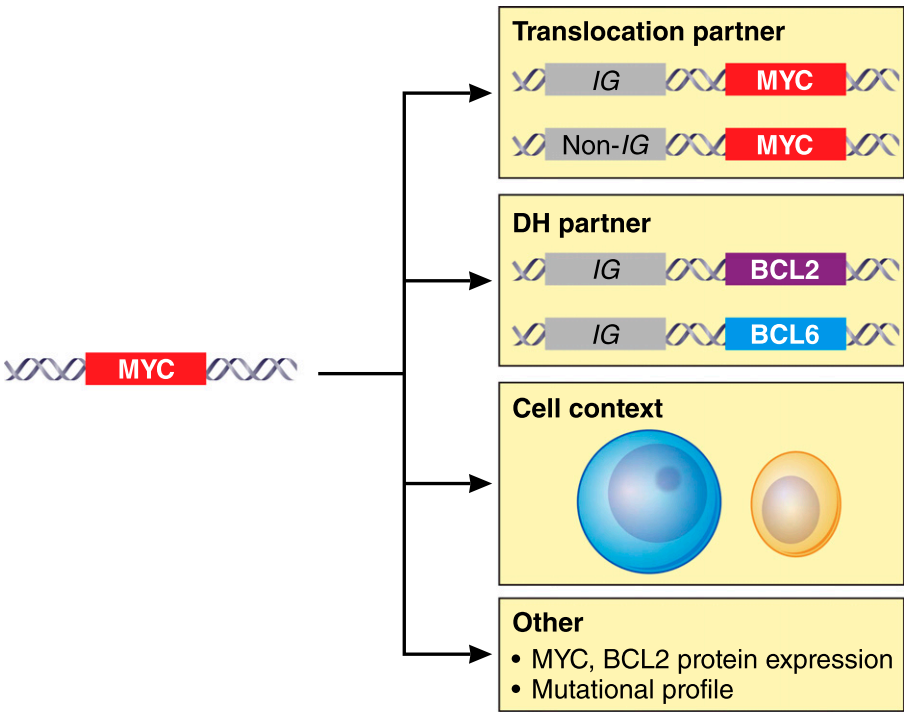
In this issue of *Blood*, Copie-Bergman et al demonstrate that *MYC* rearrangements (*MYC*-Rs) with *IG* genes, but not with other partner genes, have a negative prognostic impact in patients with diffuse large B-cell lymphomas (DLBCLs) treated with immunochemotherapy.[1]

MYC is a powerful oncogene involved in the pathogenesis of aggressive lymphoid neoplasms usually activated by gene translocations.[2] *MYC* translocations are considered the primary genetic event in Burkitt lymphoma (BL) but they also occur in 5% to 15% of DLBCLs, 30% to 50% of B-cell lymphomas (BCLs) unclassified with features intermediate between DLBCL and BL (BCLu), and a small proportion of DLBCLs transformed from small BCLs.[2] *MYC* alterations commonly occur in the context of other oncogenic events that seem to cooperate in the transformation process. Interestingly, *MYC* translocations in DLBCL are frequently associated with *BCL2* or, to a lesser extent, *BCL6* translocations, in the so-called "double-hit" (DH) lymphomas (see figure).



The biological effect of *MYC* translocation in DLBCL may be modulated by additional parameters that include the *IG* or non-*IG* partner gene involved in the translocation, the association with an additional translocation of the *BCL2* or *BCL6* genes in the so-called DH, the tumor cell context in which the alteration occurs such DLBCL, GCB or ABC, BCLu, and other factors such as the MYC or BCL2 protein levels. Additional studies are needed to explore other aspects such as the influence of somatic mutations in the tumor. Professional illustration by Patrick Lane, ScEYEnce Studios.

MYC translocations in DLBCL have recently been reported to identify a subset of patients with an unfavorable prognosis. The failure of current immunochemotherapy protocols to control the disease in these patients has motivated the development of new therapies that may overcome the adverse clinical impact of this genetic alteration.[3] However, one of the major challenges in advancing this perspective is understanding the complex biological mechanisms underlying the relationship between *MYC* alterations and the behavior of the tumors. Although most studies highlight the adverse impact of *MYC* translocations in DLBCL, some reports have provided conflicting results questioning whether *MYC* translocation as a single hit (SH) or its frequent association with *BCL2* or *BCL6* (DH) alterations is responsible for the aggressive behavior.[4] Some studies have suggested that the *BCL6* translocation in DH lymphomas may not have the same meaning as *BCL2* alterations.[5] On the other hand, some patients carrying *MYC* translocations or even DH alterations survive for long periods of time, raising the possibility that additional factors may modulate the adverse effect of *MYC* activation.[4]

The analysis of the literature is difficult. Many studies are retrospective and analyze patients treated with and without immunochemotherapy or combine primary, transformed, and relapsed DLBCL with *MYC* translocations. The distinctions between DLBCL and BCLu or the molecular

subtypes of DLBCL, germinal center B-cell–like (GCB) or activated B-cell type (ABC), are not always considered. In addition, preliminary studies suggest that some biological aspects such as the partner gene in the *MYC* translocation or the levels of MYC or BCL2 protein expression may also influence tumor behavior.[2,4,6]

The interplay of so many variables and the relative low frequency of aggressive lymphomas with *MYC* alterations make the development of appropriate studies challenging. However, this is exactly what Copie-Bergman and colleagues do in their study.[1] The authors concentrated (in the evaluation of the *MYC* translocation partner, *IG* vs non-*IG* gene) on the outcome of 574 patients with DLBCL treated with immunochemotherapy in the context of clinical trials. They started using a *MYC* break-apart fluorescence in situ hybridization probe to detect any *MYC* translocation followed by *IGH*, *IGK*, and *IGL* fusion probes to confirm whether the partner was an *IG* or non-*IG* gene. *MYC* analysis was combined with the investigation of *BCL2* and *BCL6* translocations. *MYC*-Rs were found in 9% of the cases with a similar distribution of *IG* (48%) or non-*IG* (52%) as partner genes. Interestingly, only the rearrangement with *IG* had a negative effect on the outcome of the patients, and this impact was seen in cases with isolated *MYC* translocation and also in DH tumors. Concordant with previous messenger RNA studies,[7] the authors found significantly higher MYC protein expression in *MYC-IG* than in *MYC*-non-*IG* translocated cases, suggesting that MYC levels and its transcriptional regulator partner may be relevant in the behavior of the tumor.

The study further clarifies other controversial issues. The prognostic impact of *MYC*-SH and *MYC*-DH was only observed in DLBCL with a GCB phenotype, suggesting that *MYC* activation may be more relevant in this subset of DLBCL. Intriguingly, *MYC*-SH translocations but not *MYC*-DH had an independent prognostic value from the International Prognostic Index or cell-of-origin classification. However, when *MYC/BCL6*-DH cases were excluded, then *MYC/BCL2*-DH also had an independent poor prognostic impact. The study included only 7 cases with *MYC/BCL6*-DH but, interestingly, 6 of them were non-GCB and had a tendency to better prognosis than cases with *MYC/BCL2*-DH, which occurs almost exclusively in GCB tumors. Previous reports on the prognostic value of *MYC/BCL6*-DH have been controversial,[5,8] but the findings in the current study suggest that *MYC/BCL6* may have a different biological meaning than *MYC/BCL2* in DH tumors.

One intriguing aspect in the Copie-Bergman et al study is the better-than-expected outcome of patients with *MYC* alterations, independent of the translocated partner or subtype of DH lesions, compared with the poor outcome reported in the majority of previous publications.[1-4] As the authors recognize, the selection of patients from clinical trials may represent a bias that excludes patients with a poor performance status from being eligible for the trials. In fact, virtually all cases in their study had DLBCL morphology and, upon review, only 4 cases qualified for BCLu. This is a subset of cases with frequent DH lesions and very aggressive behavior. This observation would also support previous studies suggesting that the morphology of the tumor (DLBCL vs BCLu) may be an additional element that also matters in the evaluation of the effect of *MYC* alterations.[4,9]

In summary, Copie-Bergman et al and other studies are starting to clarify the different factors, such as gene translocation partners, protein expression, or tumor subtypes, that may modulate the biological and clinical effect of *MYC* translocations in aggressive lymphomas. Understanding their interplay is essential to fulfilling the goal of providing the most appropriate therapy. However, the role of other factors, such as the profile of somatic mutations,[10] will also most probably be needed to complete this complex landscape.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Copie-Bergman C, Cuillière-Dartigues P, Baia M, et al. *MYC-IG* rearrangements are negative predictors of survival in DLBCL patients treated with immunochemotherapy: a GELA/LYSA study. *Blood.* 2015;126(22):2466-2474.

2. Ott G, Rosenwald A, Campo E. Understanding *MYC*-driven aggressive B-cell lymphomas: pathogenesis and classification. *Blood.* 2013;122(24):3884-3891.

3. Dunleavy K. Double-hit lymphomas: current paradigms and novel treatment approaches. *Hematology Am Soc Hematol Educ Program.* 2014;2014:107-112.

4. Swerdlow SH. Diagnosis of 'double hit' diffuse large B-cell lymphoma and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma: when and how, FISH versus IHC. *Hematology Am Soc Hematol Educ Program.* 2014;2014:90-99.

5. Tzankov A, Xu-Monette ZY, Gerhard M, et al. Rearrangements of MYC gene facilitate risk stratification in diffuse large B-cell lymphoma patients treated with rituximab-CHOP. *Mod Pathol.* 2014;27(7):958-971.

6. Pedersen MØ, Gang AO, Poulsen TS, et al. MYC translocation partner gene determines survival of patients with large B-cell lymphoma with MYC- or double-hit MYC/BCL2 translocations. *Eur J Haematol.* 2014;92(1):42-48.

7. Aukema SM, Kreuz M, Kohler CW, et al; Molecular Mechanisms in Malignant Lymphomas Network Project. Biological characterization of adult MYC-translocation-positive mature B-cell lymphomas other than molecular Burkitt lymphoma. *Haematologica.* 2014;99(4):726-735.

8. Pillai RK, Sathanoori M, Van Oss SB, Swerdlow SH. Double-hit B-cell lymphomas with BCL6 and MYC translocations are aggressive, frequently extranodal lymphomas distinct from BCL2 double-hit B-cell lymphomas. *Am J Surg Pathol.* 2013;37(3):323-332.

9. Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent *BCL2* and *MYC* translocations: the critical factors associated with survival. *Blood.* 2009;114(11):2273-2279.

10. Momose S, Weißbach S, Pischimarov J, et al. The diagnostic gray zone between Burkitt lymphoma and diffuse large B-cell lymphoma is also a gray zone of the mutational spectrum. *Leukemia.* 2015;29(8):1789-1791.

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● ● ● PHAGOCYTES, GRANULOCYTES, AND MYELOPOIESIS

Comment on Pereira-Lopes et al, page 2502

DNA damage response impacts macrophage functions

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In this issue of *Blood*, Pereira-Lopes et al demonstrate that a defect in a DNA damage response (DDR) component alters homeostasis of macrophages and their inflammatory responses.[1]