EDITORIAL

TP53 binding domain mutations are bad news in Burkitt lymphoma

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In this issue of *Haematologica*, Martire *et al*. has elegantly demonstrated that besides the use of rituximab in chemo-immunotherapy backbone regimens, minimal disseminated disease (MDD) at diagnosis and *TP53* binding domain mutations are associated with a significantly decreased progression-free survival (PFS) in children, adolescents and young adults (CAYA) with Burkitt lymphoma (BL).[1] We and others have previously demonstrated that the addition of rituximab to CAYA with advanced stage BL significantly increases event-free survival (EFS).[2-5] Our group previously demonstrated that 13q14.3 deletions and potentially deletion of Deleted in Lymphocytic Leukemia 1 (DLEU1) is associated with a significantly decreased EFS in CAYA with BL.[6,7] In this recent study, Martire *et al*. and her team from the University of Padova analyzed 214 cases of pediatric BL between 1999-2022, for whom both tumor tissue and bone marrow and/or peripheral blood at diagnosis were available, to perform *TP53* DNA binding domain mutation studies, utilizing Sanger sequencing of hot spot exons 5 to 8 and molecular disease dissemination.[1] They demonstrated that approximately 40% of patients possessed a *TP53* DNA binding mutation, which multivariate analysis showed was specifically associated with a significant decrease in 2-year PFS (91±3% *vs*. 76±5%; *P*<0.005). When combining *TP53* DNA binding mutation plus the presence of MDD at diagnosis, the 2-year PFS was significantly decreased compared to the subset without *TP53* binding domain mutations and MDD (92±3% *vs*. 70±7%; *P*<0.01). This same subgroup possessing both MDD and TP53 binding domain mutations was also associated with a significantly decreased 2-year overall survival (OS). Furthermore, in the subgroup with a *TP53* binding domain mutation and MDD but not receiving rituximab, the 2-year PFS was significantly decreased compared to those without a *TP53* DNA binding mutation, without MDD, and without rituximab administration (88±4% *vs*. 75±6%; *P*<0.02).

TP53 is a gene located on chromosome 17 (17p13.1) and encodes for a 53-kDa protein. The gene has 11 exons and codes for an mRNA of 2.5Kb and a protein of approximately 393 amino acids. TP53 is a master negative regulator of cell proliferation and a positive regulator of cell apoptosis in response to DNA damaging agents. In fact, *TP53* is the most commonly mutated gene in human cancer, both inherited and sporadic subtypes. Importantly, Li-Fraumeni syndrome is a multicancer predisposition syndrome that is characterized by constitutional *TP53* mutations.[8] TP53 is a nuclear phosphoprotein and has a sequence-specific DNA binding activity, and functions both as a transcriptional activator and repressor and, in part, regulates whether cells undergo cell cycle arrest and repair, or enter into repetitive senescence. The loss of TP53 function is associated with significantly decreased outcomes in patients with a number of malignancies, including lung, breast, colorectal, melanoma, and some hematopoietic cancers. Mutations in *TP53* in tumors compromise its role in tumor cell surveillance and triage, facilitating mutated tumor cells to survive and generate new and more malignant subtypes. *TP53* mutations in numerous cancers have resulted in the labeling of this gene as a classical tumor suppressor gene.[9] In this study, Martire *et al*. also demonstrated that biallelic abnormalities were significantly associated with a decreased 2-year PFS and OS compared to monoallelic abnormalities. While the types of mutations were subdivided by both mutations in exons 5-8 and by subtypes of mutations (missense mutations, nonsense mutations, in-frame deletions, frame shift and single nucleotide variant), the numbers were too small to determine whether specific mutations and/or exon location were more prognostic. The multivariate analysis included age, gender, bone marrow, central nervous system, risk group, stage, MDD and use of rituximab. However, only *TP53* DNA binding mutations and treatment with rituximab were significant variables (*P*<0.024 or *P*<0.0318, respectively). Elevated lactate dehydrogenase, a previous well-known independent prognostic

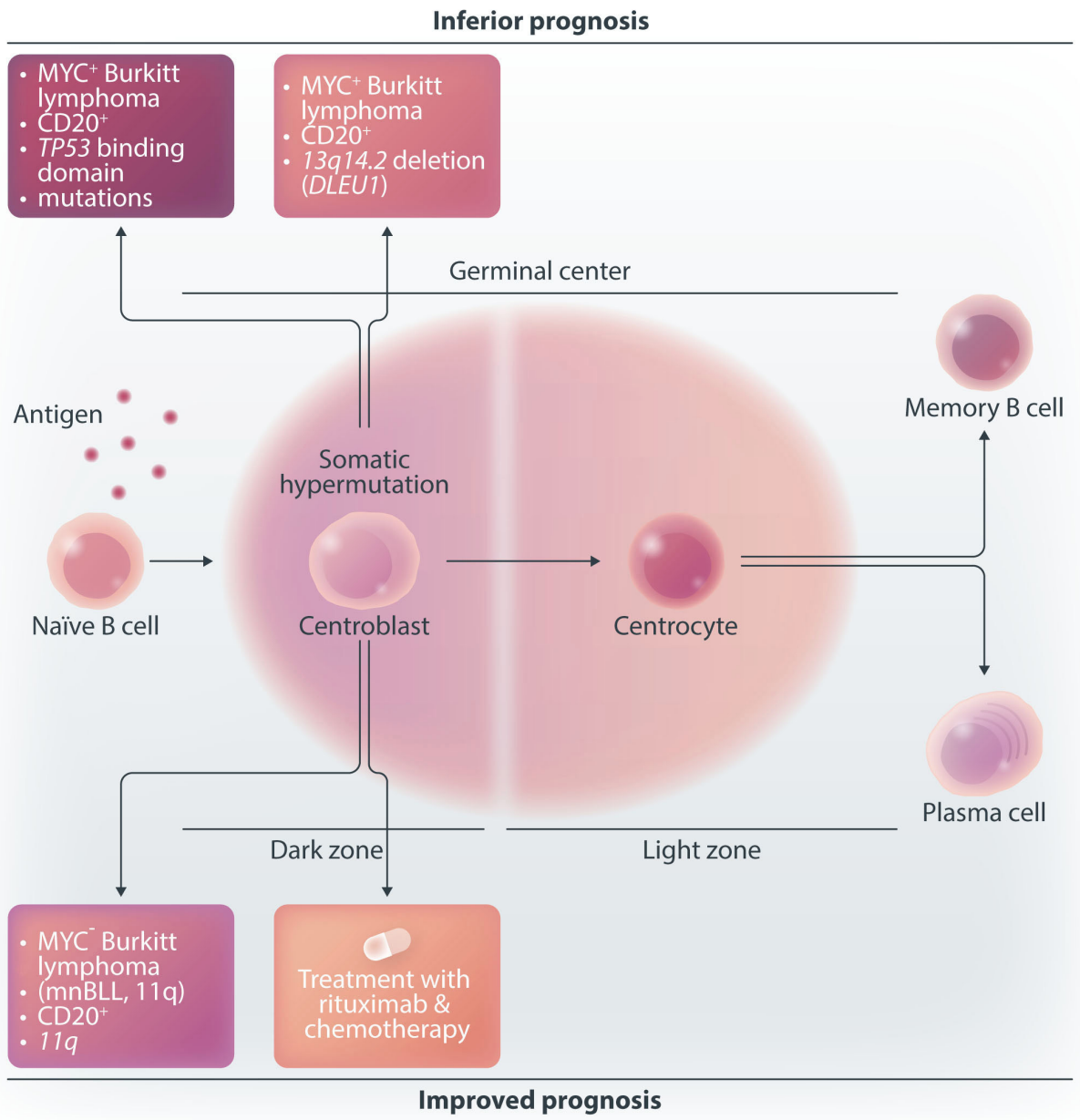

Figure 1. Genomic changes associated with improved and inferior outcome in subsets of children, adolescents and young adults with Burkitt lymphoma.

factor, however, was not included in this recent multivariate analysis.[2-4]

This important contribution to the field expands our existing knowledge of the heterogeneity of the genomic makeup of CAYA with BL. These *TP53* DNA binding domain mutations, as identified in this study, along with the 13q14.1 (DLEU1) deletions and the MYC Burkitt-like lymphoma (BLL) associated with 11q aberrations (mbBLL, 11q) are all subsets with alterations in the genomic landscape of CAYA with BL that are derived from germinal center centroblasts (Figure 1). The first two, *TP53* DNA binding mutations and 13q14.3 deletions, are associated with an inferior prognosis, whereas the latter mbBLL-11q is associated with a significant improvement in the prognosis of CAYA with BL.[1,6,7,10] Hopefully, future investigations will elucidate the exact mechanisms associated with either decreased or increased survival with each of these genomic abnormalities in CAYA with BL. This contribution by Martire *et al*. will help widen our understanding of both the genetic heterogeneity of BL in CAYA and the importance of targeted antibody immune-based therapy to overcome and/or circumvent known risk factors in those subtypes previously associated with an inferior outcome.

Disclosures

MSC currently serves as a consultant for Jazz Pharmaceuticals and Abbvie, and is on the Speakers Bureau for Jazz Pharmaceuticals and Sobi.

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