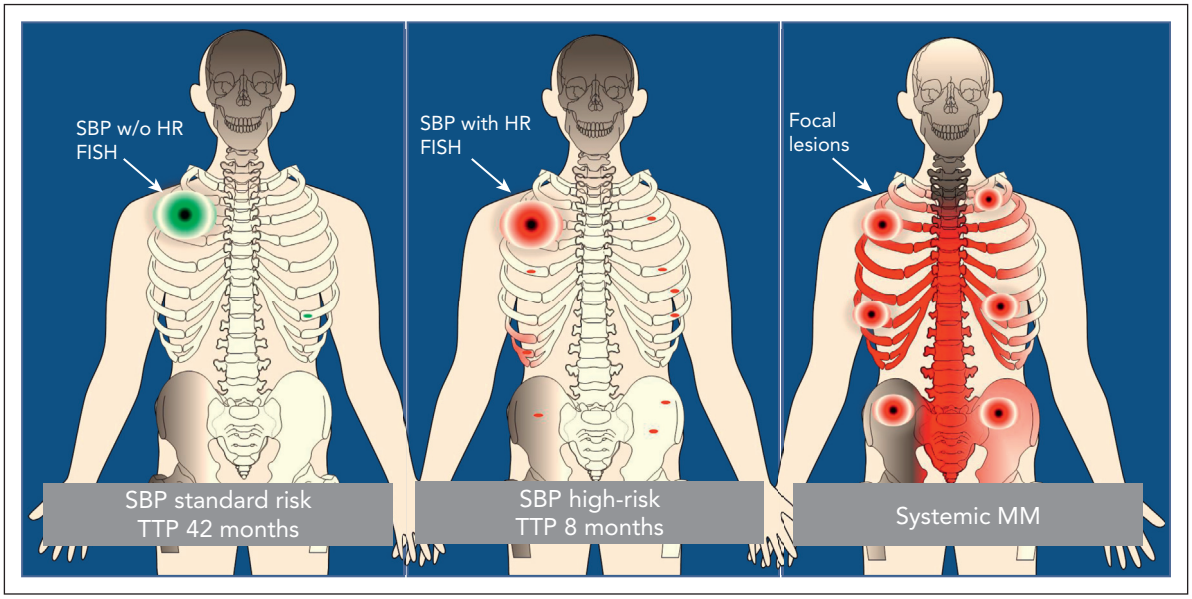

Dissemination of clonal plasma cells in solitary bone plasmacytoma and MM. In MM, focal lesions are usually superimposed on diffuse infiltration patterns, whereas in SBP the potential for invasion and dissemination at distant bone marrow sites and, as a consequence, the time to progression (TTP) are associated with high-risk (HR) cytogenetics.

not least, there are no data yet that indicate there is a long-term negative impact of radiation in patients with SBP, but ionizing radiation certainly has mutagenic potential.[7]

Together, the data reported by Yadav et al could impact clinical decision making in SBP. We hope that future studies will successfully address remaining open questions, including a solution for patients with insufficient diagnostic material and evaluating the role of high-risk cytogenetics in the potential to invade distant bone marrow sites.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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LYMPHOID NEOPLASIA

Comment on Liu et al, page 1879

EGR1 changes course in B-cell lymphoma

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In this issue of *Blood*, Liu et al[1] describe a new route to acquired ibrutinib resistance via the transcription factor early growth response gene 1 (EGR1), which induces metabolic changes toward oxidative phosphorylation (OXPHOS) in activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL) and mantle cell lymphoma (MCL).

The authors map out the contribution of EGR1 expression levels to ibrutinib resistance in lymphoma cells and show a link between EGR1 and a metabolic change toward OXPHOS via pyruvate dehydrogenase phosphatase catalytic subunit 1 (PDP1). Therefore, targeting OXPHOS metabolism with metformin or IM156 may be a therapeutic strategy to overcome ibrutinib resistance in relapsed or refractory B-cell lymphoma. Thus, EGR1 does change the metabolic course of B-cell lymphoma and is the helmsman for OXPHOS, but can we utilize these findings to take the wind out of the lymphoma sails?

Ibrutinib changed B-cell lymphoma treatment, and multiple clinical studies demonstrated that patients with relapsed or refractory B-cell lymphoma treated with ibrutinib had longer survival compared with those receiving other therapies.[2-4] However, patients

responsive to ibrutinib often develop resistance with disease progression and a poor prognosis.[5] Therefore, targeting this resistance is an area of active research. The reasons for resistance are multifaceted and include mutations, activation of signaling pathways, changes in the tumor microenvironment, and metabolic changes. OXPHOS is an active metabolic pathway in many solid tumors and lymphomas,[6] and several studies identified a shift toward OXPHOS metabolism being associated with ibrutinib resistance in MCL and ABC-DLBCL.[7-9]

Liu et al found that EGR1 protein levels are upregulated in ibrutinib-resistant ABC-DLBCL and MCL cell lines and even further upregulated when these resistant cell lines are exposed to ibrutinib. The latter was also seen in samples from patients with MCL upon ibrutinib treatment. Ibrutinib not only induced EGR1 expression, but further overexpression and knockdown experiments revealed that high EGR1 levels also contribute to ibrutinib resistance in ABC-DLBCL cell lines. The mechanism behind the EGR1 overexpression is EGR1 self-regulation by binding to its own promoter region. *EGR1* is a target of transcription factor 4 (TCF4), a known epigenetic driver for ibrutinib resistance. As previously described, metabolic reprogramming toward OXPHOS dependency is characteristic of ibrutinib resistance in MCL,[8,9] and Lui et al extended these findings to their ABC-DLBCL cell lines and saw augmented mitochondrial respiration. This is caused by increased PDP1 (a target of EGR1) expression via transcriptional activation, leading to enhanced pyruvate dehydrogenase activity and accelerated adenosine triphosphate production (see the online visual abstract from Liu et al[1]).

Apart from the detailed mechanism of OXPHOS upregulation in ibrutinib-resistant cells, the authors targeted this pathway with metformin as an OXPHOS inhibitor. Metformin treatment was able to restore ibrutinib sensitivity in resistant ABC-DLBCL cell clones and furthermore sensitized primary resistant ABC-DLBCL cell lines to ibrutinib. The in vivo model with metformin given with ibrutinib treatment showed a significant impact on tumor volume and weight only in ABC-DLBCL cell line xenografts. However, the more potent OXPHOS inhibitor IM156, a newly developed metformin derivative, was able to synergize with ibrutinib in all analyzed cells in vitro. Moreover, the drug combination of ibrutinib with IM156 achieved significant antitumor effects in a xenograft model derived from a patient with MCL compared with the monotherapy with either drug.

Based on these data, many questions arise. Will these findings be relevant only for patients who develop a resistance to ibrutinib, or, as part of the data suggests, might all patients who showed no initial response to ibrutinib benefit from combination therapy, targeting Bruton tyrosine kinase (BTK) and OXPHOS simultaneously? Since ibrutinib is no longer the only BTK inhibitor in use, can these findings be translated to other BTK inhibitors and to other disorders, which are currently treated with BTK inhibitors? One pressing question for the clinical applicability of these data is determining the optimal treatment strategy. To answer these and many other questions arising from the findings of Lui et al, further preclinical and clinical studies will be necessary as we await the sinking of ibrutinib resistance.

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

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PLATELETS AND THROMBOPOIESIS

Comment on Verdier et al, page 1895

Genetics of predicted platelet reactivity

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In this issue of *Blood*, Verdier et al pioneer a new method to predict platelet reactivity from complete blood count data, and they apply it to identify associated genetic variants and explore associations with thrombotic diseases.[1]

Platelets play a critical role in hemostasis and thrombosis, and antiplatelet drugs are widely used in cardiovascular disease prevention and treatment. There is interindividual variability in platelet reactivity, as measured by platelet aggregation responses to various agonists.[2] Identifying the genetic determinants of platelet reactivity could lead to a greater understanding of these differences and to the identification of additional targets for new antiplatelet drugs. Traditional methods for measuring platelet reactivity are difficult to implement at large scales,