

a modulator of MCL1 and glucocorticoid resistance. *Cancer Cell*. 2006;10(4):331-342.

9. Hulleman E, Kazemier KM, Holleman A, et al. Inhibition of glycolysis modulates prednisolone resistance in acute lymphoblastic leukemia cells. *Blood*. 2009;113(9):2014-2021.

10. Real PJ, Tosello V, Palomero T, et al. Gamma-secretase inhibitors reverse glucocorticoid resistance in T cell acute lymphoblastic leukemia. *Nat Med*. 2009;15(1):50-58.

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● ● ● LYMPHOID NEOPLASIA

Comment on Liu et al, page 284

Novel target to kill CLL

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In this issue of *Blood*, Liu et al report on OSU-T315, a new agent that specifically disrupts the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway and shows high proapoptotic activity against chronic lymphocytic leukemia (CLL) cells, which may indicate a potential therapeutic application in this disease.¹

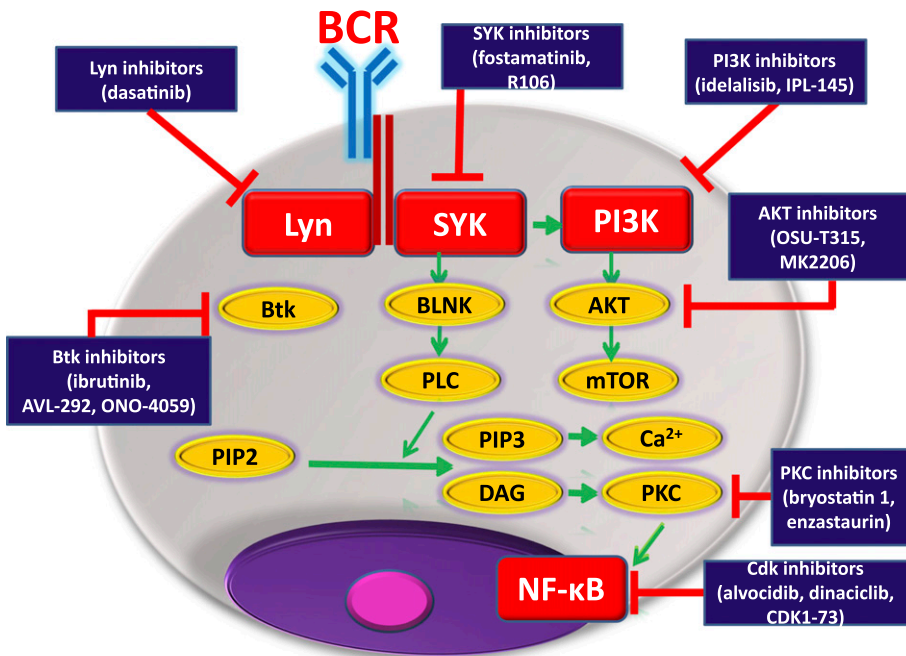
Great progress has been made in the diagnosis and treatment of CLL, but this type of leukemia still remains incurable, and the introduction of new drugs and new therapeutic strategies are still awaited. For the last 20 years, significant progress in molecular biology has resulted in better characterization and understanding of the biology and prognosis of CLL. Accumulating evidence

supports the critical role played by B-cell receptor (BCR) activation in the pathogenesis of CLL and has provided new opportunities for the development of innovative, more effective therapies. Recently, several small molecular kinase inhibitors targeting the proximal BCR signaling pathway, including Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, and phosphatidylinositol 3-kinase

p110δ (PI3Kp110δ) inhibitor, idelalisib, have been developed (see figure). These drugs are part of a promising new strategy for the effective targeted treatment of CLL and have been recently approved by the US Food and Drug Administration.^{2,3}

Among the new therapies intended for CLL, much attention is being paid to the implementation of agents with a high potential for triggering apoptosis of tumor cells.⁴ The PI3K/AKT signaling pathway plays a pivotal role in regulating multiple cellular events supporting the survival of CLL B cells. In CLL, activation of the PI3K/AKT pathway has an important role in the generation of the proliferative pool, and the pharmacological compounds that disrupt this pathway may have significant antiproliferative activity.⁵ Studies based on the coculture of CLL cells with marrow stromal cells show that PI3K/AKT signaling plays an important role in the activation of both cell types during their interactions that support survival of CLL tumor cells.⁶ OSU-T315 is an inhibitor of the PI3K/AKT pathway, which exhibits high in vitro potency against a panel of prostate and breast cancer cell lines.⁷ Liu et al report their results of a study comparing the activity of OSU-T315 in both CLL-derived cell lines and primary CLL cells with its action in normal lymphocytes. They document a unique mechanism of OSU-T315 action. Namely, the compound directly abrogates AKT signaling by preventing the translocation of AKT kinase into lipid rafts. Importantly, in this mechanism, the activation of receptor-associated kinases remains unaltered. As a consequence, OSU-T315 induces caspase-dependent apoptosis by suppressing BCR, CD49d, CD40, and Toll-like receptor 6-mediated AKT activation in CLL cells. This mechanism is independent of the integrin-link kinase.¹ Moreover, in a transplant TCL1 mouse model, OSU-T315 prolongs the survival of leukemic mice by the selective targeting of CLL cells and sparing of normal B or T lymphocytes.

In addition to OSU-T315, other AKT inhibitors exert antileukemic activity. The best example is MK2206, a highly selective oral allosteric AKT inhibitor found to exert the in vitro efficacy of MK2206 on CLL B-cell survival.⁸ MK2206 abolishes phosphorylation of AKT^{S473}, significantly



BCR-signaling pathway showing kinase inhibitors, already approved or potentially useful in CLL, and their biological targets. BLNK, B-cell linker; Cdk, cyclin-dependent kinase; DAG, diacylglycerol; Lyn, member of the Src family of protein tyrosine kinases; NF-κB, nuclear factor κB; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PKC, protein kinase C; PLC, phospholipase C; mTOR, mammalian target of rapamycin.

decreasing the activation of the AKT target, p70S6K, without affecting the p85 unit of PI3K, and in turn activates caspase-dependent apoptosis of CLL cells. Moreover, MK2206 selectively inhibits BCR-induced CCL3, CCL4, CCL2, and interleukin-2R α production, most probably by abrogating AKT and extracellular signal-regulated kinase. Importantly, MK2206 kills CLL cells and spares healthy lymphocytes, in a similar way to OSU-T315.⁸

Ibrutinib and idelalisib have been found to demonstrate a remarkable clinical response in CLL patients. However, recent studies have identified patients refractory to these agents and characterized a BTK mutation (*BTKC481S*) responsible for ibrutinib resistance.^{9,10} A way of overcoming the ibrutinib resistance demonstrated by these patients is urgently needed. Recent studies suggest that therapeutic intervention with other kinase inhibitors, such as idelalisib or spleen tyrosine kinase (SYK) inhibitors, may shut down BCR signaling and inhibit CLL proliferation in patients who have acquired the *BTKC481S* mutation.⁹ However, these drugs inhibit the BCR signaling pathway at proximal kinases, and some CLL patients can be refractory to both ibrutinib and idelalisib. For those patients, compounds such as OSU-T315, which directly abrogates AKT activation without altering the activation of receptor-associated kinases, can be particularly useful.

In conclusion, OSU-T315 is a new compound showing a specific, novel mechanism of abrogating the AKT pathway and inhibition of BCR activity in the leukemic cell. Therefore, this compound can be potentially useful in the treatment of high risk CLL, including patients with *del(17p13.1)*, unmutated *IGVH*, or those who may be resistant to ibrutinib.

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

REFERENCES

- Liu T-M, Ling Y, Woyach JA, et al. OSU-T315: a novel targeted therapeutic that antagonizes AKT membrane localization and activation of chronic lymphocytic leukemia cells. *Blood*. 2015;125(2):284-295.
- Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014; 371(3):213-223.
- Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110 δ , for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014;123(22):3390-3397.

- Chen R, Plunkett W. Strategy to induce apoptosis and circumvent resistance in chronic lymphocytic leukaemia. *Best Pract Res Clin Haematol*. 2010;23(1):155-166.
- Palacios F, Abreu C, Prieto D, et al. Activation of the PI3K/AKT pathway by microRNA-22 results in CLL B-cell proliferation [published online ahead of print May 14, 2014]. *Leukemia*. doi:10.1038/leu.2014.158.
- Edelmann J, Klein-Hitpass L, Carpinteiro A, et al. Bone marrow fibroblasts induce expression of PI3K/NF-kappaB pathway genes and a pro-angiogenic phenotype in CLL cells. *Leuk Res*. 2008;32(10): 1565-1572.
- Lee SL, Hsu EC, Chou CC, et al. Identification and characterization of a novel integrin-linked kinase inhibitor. *J Med Chem*. 2011;54(18):6364-6374.

- Ding W, Shanafelt TD, Lesnick CE, et al. Akt inhibitor MK2206 selectively targets CLL B-cell receptor induced cytokines, mobilizes lymphocytes and synergizes with bendamustine to induce CLL apoptosis. *Br J Haematol*. 2014;164(1):146-150.
- Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370(24):2286-2294.
- Cheng S, Guo A, Lu P, Ma J, Coleman M, Wang YL. Functional characterization of BTK(C481S) mutation that confers ibrutinib resistance: exploration of alternative kinase inhibitors. *Leukemia*. 2014.

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● ● ● MYELOID NEOPLASIA

Comment on Chen et al, page 327, and on Kameda et al, page 304

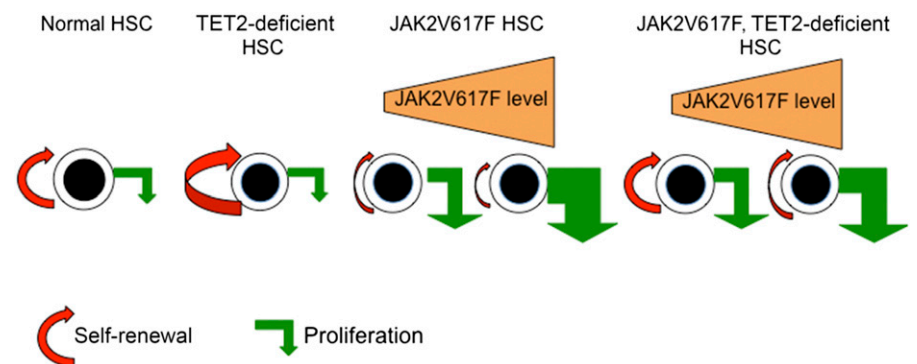
TET2 loss, a rescue of JAK2V617F HSCs

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In this issue of *Blood*, Chen et al¹ and Kameda et al² demonstrate that Tet2 loss has 2 effects in *Jak2V617F* mice: it increases both the severity of the myeloproliferative disorders and the self-renewal properties of the *Jak2V617F* hematopoietic stem cells (HSCs).

BCR-ABL-negative classical myeloproliferative neoplasms (MPNs) include 3 disorders—essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis—which are driven by *JAK2* activation. *JAK2V617F*, a gain-of-function mutation, is the most frequent genetic alteration. It is present in more than 70% of MPNs and leads to

a cytokine hypersensitivity.³ *JAK2V617F* is really the driver of the disease because it induces a myeloproliferative disorder in all tested murine models, sometimes with extremely different phenotypes that can range from a benign thrombocytosis to a lethal myelofibrosis.³ This range is well illustrated in the 2 present studies: the model used by Chen et al is an inducible *Jak2V617F*



Model for the regulation of HSC self-renewal and proliferation by TET2 loss, JAK2V617F, and the combination of JAK2V617F and TET2 loss. TET2 loss increases the self-renewal of HSCs without significant effects on their proliferation, explaining that TET2-deficient HSCs outcompete normal HSCs and lead to clonal hematopoiesis. The effects of JAK2V617F on HSCs are dependent on the level of expression and yet-unknown parameters. At low levels of expression, JAK2V617F induces the proliferation of HSCs but slightly decreases self-renewal. The proliferation effect being predominant, JAK2V617F HSCs are capable of outcompeting wild-type HSCs. At high levels of expression, JAK2V617F may more profoundly alter the functions of HSCs. The TET2 loss restores the function of JAK2V617F by increasing self-renewal. The restoration is complete or incomplete depending on the defect of the JAK2V617F HSCs. Overall, TET2 loss increases the fitness of JAK2V617F to induce an MPN.