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A targetable cue in T-cell malignancy

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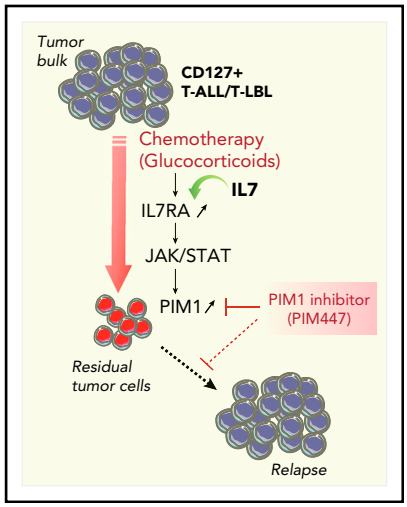
In this issue of *Blood*, De Smedt et al demonstrate that glucocorticoid treatment of a subset of T-cell acute lymphoblastic leukemia/T-cell acute lymphoblastic lymphoma (T-ALL/T-LBL) cells upregulates *PIM1* expression, creating a synergistic vulnerability and potent antileukemic effect with PIM1 inhibitors in a preclinical model.[1]

Initially described in the context of a murine T-cell lymphoma, PIM1 is an oncogenic serine/threonine kinase involved in several cellular processes, including cell-cycle progression, transcription, apoptosis, and drug resistance. *PIM1* is transcriptionally activated by the canonical JAK-STAT pathway in response to extracellular ligand stimulation. Not surprisingly, activating mutations within the IL7RA-JAK-STAT pathway in human T-ALL/T-LBL were reported to cooperate in activating *PIM1* in these cells. In rare cases, the *PIM1* locus itself can be activated by chromosomal rearrangements. Indeed, De Smedt et al recently identified the *TCRβ-PIM1* translocation in a case of pediatric T-LBL and demonstrated the preclinical benefit of using a second-generation PIM1 inhibitor combined with a glucocorticoid to treat such patients.[2] De Smedt et al report an unexpected mechanism of *PIM1* activation and propose that a broader subset of CD127$^+$ T-ALL/T-LBL patients lacking known mutations of the IL7RA pathway could benefit from treatment with a PIM1 inhibitor.



Synthetic lethality approach to killing residual tumor cells in CD127$^+$ T-ALL/T-LBL. Glucocorticoids efficiently reduce the tumor burden and induce acute in vivo PIM1 expression in residual tumor cells through the cell-non-autonomous activation of the IL7RA/JAK-STAT signaling pathway. Combination therapy with the PIM inhibitor PIM447 allows for a synergistic antileukemic effect on residual tumor cells.

By using patient-derived xenograft (PDX) models of CD127$^+$ T-ALL/T-LBL, the authors uncovered a cell-non-autonomous mechanism that occurs in drug-resistant cells after treatment with glucocorticoids. They demonstrated that glucocorticoids upregulate the *IL7RA/JAK-STAT/PIM1* axis. Two notable features emerge from this study. First, glucocorticoid-triggered upregulation of *PIM1* occurs in the absence of detectable known mutations in genes of the interleukin-7 receptor (IL-7R) pathway, indicating that *PIM1* activation may not be the result of the well-studied mutational burden within the tumor. Second, *PIM1* upregulation was observed exclusively in PDX samples that respond to IL-7 stimulation and did not occur in nonresponders, which strongly suggests that *PIM1* upregulation was the result of IL-7 signaling. In line with this hypothesis, an analysis of published chromatin immunoprecipitation sequencing (ChIP-seq) data shows that the glucocorticoid receptor NR3C1 occupies the *IL7RA* but not the *PIM1* locus, thereby upregulating *IL7RA* expression.

Finally, PIM1 upregulation in residual leukemic blasts after chemotherapy is transient, further supporting the view that the upregulation is not due to constitutive mutations within the pathway in leukemic blasts. Remarkably, this cell-non-autonomous mechanism provides a window of therapeutic opportunity for killing drug-resistant cells with PIM1 inhibitors (see figure). Indeed, using an elegant in vivo preclinical approach, the authors demonstrated a synergistic antileukemic effect of combination therapy of glucocorticoids and the PIM inhibitor PIM447. A survey of clinical trials indicates that several PIM1 inhibitors are currently in clinical trials for myeloma, myelofibrosis and, more recently, for diffuse large B-cell lymphoma and solid tumors. The study by De Smedt suggests that PIM447 could be a new drug candidate for clinical treatment of CD127$^+$ T-ALL/T-LBL patients.

In addition to its translational impact, the work by De Smedt et al brings into question whether there are additional mechanisms of drug resistance that should be considered. First, despite the clear synergistic antileukemic effect of PIM447 and glucocorticoids, as well as the substantial delays in leukemia onset in preclinical models, this 2-drug combination does not prevent long-term leukemia development in PDX models. This could be a result of the presence of a persisting minor subclone within residual leukemic cells that is insensitive to PIM447. Given the possibility of subclonal diversity[3,4] and the emerging evidence of therapy-induced mutations in ALL,[5] drawing the genetic and the molecular landscape of leukemic cells after glucocorticoids and/or PIM447 treatment in PDX models should bring additional understanding of the biology of short- and long-term relapse. Second, tumor cell interaction with its microenvironment could modify drug response, as illustrated by the recent report in *Blood*[6] of mitochondria transfer from activated stromal cells to rescue ALL cells from drug-induced oxidative stress. The possibility of tumor cell-stromal cell interactions shaping drug response has led to the design of niche-based drug screening strategies in acute myeloid leukemia (AML)[7] and T-ALL.[8]

Last but not least, pioneering work using xenotransplantation of primary AML blasts into immune-deficient mice revealed the heterogeneity of leukemic cells and the presence of leukemic stem cells (LSCs) that are able to maintain the neoplastic process. Those original xenografting experiments clearly demonstrated that administering human cytokines to murine hosts is

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essential for human LSC engraftment.[9] In T-ALL, it was shown using PDX models that the interactions between tumor cells and their microenvironment are critical to promote leukemia progression.[10] Taken in context, the work reported by De Smedt et al is another "cue" that dependency on cell-non-autonomous signals can be a tractable vulnerability in leukemias and lymphomas.

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

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MYELOID NEOPLASIA

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To be, or not to be

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In this issue of *Blood*, Ronner and coworkers conclude that leukocytosis in patients with polycythemia vera (PV) is not a risk factor for thrombosis, but it is associated with disease evolution. To investigate these critical questions, the authors used a sophisticated statistical approach to interrogate data from a retrospective, multi-institutional cohort of 440 patients.[1]

Theories regarding the participation of leukocytes in the pathogenesis of thrombosis are very old (see figure) and are now supported by experimental findings and clinical observations. Whether there is an *affaire* between leukocytes and thrombosis in patients with PV has been long debated,[2] with conflicting results and opinions across numerous studies.[3] The question is not trivial, especially given the clinical implications of a positive association: the latter, in fact, would elevate leukocytosis to a target for treatment to decrease the risk of thrombosis. At the same time, it would provide a reliable and easy-to-obtain biomarker of thrombosis risk and effectiveness of therapy. Leukocytosis is not formally incorporated in the conventional risk score for thrombosis in PV, that relies upon age >60 years and/or history of cardiovascular events. The supportive data for the risk score are derived from retrospective studies. However, both the European LeukemiaNet (ELN)[4] recommendations and the National Comprehensive Cancer Network guidelines[5] included leukocytosis >15 × 10^9/L and progressive leukocytosis, respectively, among the indications for initiating cytoreduction in an otherwise low-risk patient with PV. Furthermore, normalization of the leukocyte count is listed among the variables for adjudicating complete or partial remission after treatment, according to the ELN and International Working Group for Myeloproliferative Research and Treatment response criteria.[6] On the other hand, leukocytosis (>10 or 15 × 10^9/L, depending on the particular study), together with age and venous thrombosis, predicted for transformation to post-PV myelofibrosis, which occurs with a cumulative incidence of 8% to 14% at 15 years.[7] Age and leukocytosis are also major determinants of the risk of PV transforming to acute leukemia, with rate of 5% to 10% at 20 years.[7] Finally, leukocytosis >15 × 10^9/L, together with age ≥67 years, thrombosis history, and *SRSF2* mutation, was a risk factor for survival among 404 molecularly characterized PV patients.[8]

The basic assumption of Ronner et al is that the role of leukocytosis in PV may have been misinterpreted in retrospective series that used a single time point, rather than time-dependent data. The novelty of the work of Ronner et al relies on the use of a unique statistical approach, group-based trajectory modeling (GBTM), largely employed in social and behavioral sciences. The GBTM approach better demonstrates the evolution of an outcome over time, based on the principle that meaningful subgroups within a population exist, and follow distinctive developmental trajectories that cannot be identified a priori by the single-point measurement of individual characteristics. To apply this approach, Ronner et al used data from 440 PV patients, collected in 10 academic US institutions, who had ≥3 clinical and hematologic records available, at least 1 of which was within the last 10 years. This data set enabled the investigators to draw trajectories for the different blood cell subsets.

According to GBTM analysis, 4 clusters of patients were identified: stable leukocyte counts at 5, 10, 15, and oscillating at 35 × 10^9/L. The lower 2 clusters accounted for 75% of the patient population. The data set was adjusted for a number of variables, including whether the patient was receiving cytoreductive therapy in the landmark trajectory period. No association between leukocyte trajectory and thrombosis emerged, whereas leukocytosis was confirmed to be associated with disease evolution, including myelofibrosis, myelodysplasia, and acute leukemia. In addition, the study confirmed the null role

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