in T- and NK-LGL, and ample material for future investigations.

Jerez et al focused on the SH2 domain in their search for mutations. However, some of the gain-of-function STAT3 mutations found in hepatocellular carcinoma are outside this domain, suggesting that all domains of the STAT3 gene should also be closely inspected before we call them truly wild-type. Detailed sequence analysis could also solve the current paradox that neither laboratory findings nor the overall survival seem to distinguish between patients with wild-type and mutant STAT3 SH2 domains.

Now that mutations in the STAT3 gene in LGL are identified, the next step is to explore the functional consequence of these alterations in CD8+ T cells and NK cells. The transduction of STAT3 mutants identified in LGL, which are presumably gain-of-function mutants, and, as a control, from Job syndrome patients, which represent loss-of-function or hypomorphic mutants, into CD8+ T cells/NK cells from healthy donors should educate us on the effect these variants have on gene expression, proliferation, and survival on cytokine withdrawal, and leukemic behavior in the form of extended survival in a xenogenic mouse model. Furthermore, such studies should uncover differences in the way T cells and NK cells handle STAT3 mutants.

Lastly, although T-LGL is characterized by the expansion of CD57+ CD8+ T cells, we observed that the LGL clone is represented in both CD57+ and in CD57- fractions. Indeed, CD57- cells lacked proliferative capacity, but were readily generated from sorted CD57- LGL cells. With the recent discovery of a stem cell memory T cell (TSCM), a burning question is whether the T-LGL clone originates in early memory cells and carries the mutant STAT3 gene. Such a finding would refocus the need to target STAT3 inhibitors on the true LGL stem cell.

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

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Live and let (MPN cells) die!

Bruno Cassinat and Jean-Jacques Kiladjian

In this issue of Blood, Lu et al show that the combination of interferon-α (IFNα) and nutlin-3 is efficient to selectively impair proliferation and differentiation of malignant hematopoietic progenitor cells (HPCs) in myeloproliferative neoplasms (MPNs) in vitro. The first mutation identified and resembled the ideal candidate for targeted therapy in MPNs. By analogy with chronic myeloid leukemia (CML), one could hope that once an oncogenic event is identified, targeted therapy would be developed, leading eventually to a curative approach. Indeed, such a strategy provided a spectacular advance in the therapy of CML with the development of tyrosine kinase inhibitors targeting the BCR-ABL oncogene. We know now that the situation is more complicated in Philadelphia-negative MPNs, as on the one hand more than 15 different mutations (MPL, TET2, ASXL1, and so on) can be found in those illnesses, and on the other, several subclones harboring mutations in genes involved in different pathways can be found in one patient’s hematopoietic cells. To date, no clear effect on the mutant allele burden of patients with JAK2V617F mutation and no impact on bone marrow fibrosis could be firmly demonstrated in JAK2 inhibitor–treated patients, although some promising preliminary results appeared in early phase trials with some of these compounds. By contrast, IFNα therapy (and particularly therapy using pegylated-IFNα-2a [peg-IFNα-2a]) resulted in significant reduction of the JAK2-mutant allele burden in addition to clinical and histopathologic responses, leading in selected patients with MPN to apparent eradication of the mutated clone with restoration of normal bone marrow morphology. Two limitations, however, may hamper the clinical use of IFNα: adverse reactions, leading to treatment discontinuation in 20% to 30% of patients in the long term; and possible resistance of subclones carrying mutations in genes other than JAK2. These limitations could be overcome using combination therapy allowing reduction of the dose of IFNα (to improve tolerance) and simultaneous targeting of multiple oncogenic pathways.

p53 is one of the most frequently mutated oncogenes in cancer. Such mutations are very rare in chronic-phase MPN but may be acquired during their evolution to acute leukemia. In addition to genotoxic mutations, wild-type p53 function can be inactivated by increased degradation after binding to murine double minute 2 (MDM2), a negative regulator of the p53 pathway. Inhibition of MDM2 results in p53 stabilization, activation of cell-cycle arrest, and apoptosis pathways, that is, restoring the ability of cancer cells that had developed mechanisms to escape from programmed cell death to die. Recently, Nakatake et al reported that JAK2V617F-mutated cells exhibit an increased p53 degradation due to an increased MDM2 protein level. In addition, they found that inhibition of MDM2/p53 binding with nutlin-3, a small molecule inhibitor of this interaction, resulted in specific inhibition of the EPO-independent growth of JAK2-mutated cells, suggesting that MDM2 inhibition could reduce the malignant clone in MPNs.
Based on these findings, and because IFNα has been reported to induce apoptosis in target cells in part through up-regulation of p53 activity, Lu et al tested the smart strategy of combining nutlin-3 with peg-IFNα-2a to study their efficacy against primary MPN cells derived from patients with polycythemia vera (PV) with JAK2V617F mutation. Results of this in vitro study show that this combination of drugs is particularly efficient to selectively target MPN–derived HPCs harboring the JAK2V617F mutation with minimal impact on normal hematopoietic cells. While IFNα has many biologic properties that may account for its efficacy in the therapy of MPNs, the authors also provide evidence for a synergistic effect of the IFNα/nutlin-3 combination in the accumulation of p53, by affecting complementary pathways.

The study by Lu et al provides proof of concept for a potential clinical benefit of the combination of low doses of peg-IFNα-2a with nutlin-3 that has to be confirmed in vivo and, potentially, in clinical trials. One important advantage of this combined therapy highlighted by the study is that very low doses of peg-IFNα-2a could be sufficient to achieve efficacy, suggesting that a higher proportion of patients could benefit from long-term IFNα therapy with better tolerance. The second interesting finding is that this combination seems to have a moderate impact on nonclonal hematopoietic cell proliferation and differentiation that could predict lower hematologic toxicity in treated patients. In addition, although this study was performed mainly in cells carrying the JAK2V617F mutation particularly prone to respond to nutlin-3, the mechanisms involved in the effects of both drugs are independent of the presence of JAK2V617F mutation. Therefore, such combined therapy could be equally efficient in all patients with MPNs regardless of the presence of a specific mutation, as suggested by the results observed by Lu et al in cells derived from a patient with myelofibrosis without JAK2 mutation. Finally, measurements of MDM2 protein levels could become a new biomarker useful in MPN management if shown to be able to select patients likely to respond to nutlin therapy or to be a reliable tool to monitor treatment efficacy on the target cells, as was shown for JAK2V617F mutation in patients treated with peg-IFNα-2a.

In addition to reducing the apoptotic response to DNA damage, JAK2V617F mutation has also been shown to induce genetic instability, and to influence gene expression through modifications of chromatin structure, mechanisms that may favor evolution to acute leukemia. Combining a nonleukemogenic agent like IFNα with nutlin-3 could also reduce the risk of acute transformation by reducing the genomic instability and the accumulation of secondary oncogenic events, and letting the MPN cells die through apoptosis. 

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Comment on Poletto et al, page 3112

GR SNP helps transform myelofibrosis

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In this issue of Blood, Poletto and colleagues examine the association of A3669G single nucleotide polymorphism (SNP) of human glucocorticoid receptor (GR) in patients with primary myelofibrosis (PMF), demonstrating a significantly higher frequency of this allele in these patients than in 2 cohorts of healthy individuals.1

The GR A3669G SNP was also associated with a higher white blood cell count, higher spleen index, and a higher frequency of peripheral blood (PB) CD34-positive cells in PMF. Furthermore, among the patients with JAK2V617F-mutated PMF, the transformation-free and overall survival were significantly shorter in patients homozygous for the GR A3669G.

Cancer susceptibility genes as well as genes that predict a higher risk of transformation from an indolent to a more aggressive state of the disease are of particular interest as these can identify patients at risk and may allow modifications in management that alleviate or delay disease-associated complications. Among hematologic malignancies, transformation from a less aggressive to a more acute status is commonly associated with a poor prognosis, giving rise to entities that are more sinister than their de novo counterparts. Transformation to a disease that phenotypically is considered to be acute myeloid leukemia (AML) is seen in patients with myeloproliferative neoplasms (MPNs) as well as myelodysplastic syndromes, and is termed “blast phase” in the former.2 Such a variant of AML is commonly insensitive to traditional cytotoxic chemotherapy, is frequently associated with a rapid decline, and can only be cured in the minority of cases using an allogeneic stem cell transplant. Therefore, identification of predictors of disease transformation as well as development of more effective therapeutic strategies in this setting is of particular importance.3

Several recent reports have examined the clinical predictors as well as potential molecular events that predispose to the transformation to AML in patients with
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