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,[10] 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.[5]

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.[2,3] 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.

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

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● ● ● MYELOID NEOPLASIA

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 *JAK2*V617F-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

PMF. In a study of 311 patients from the Mayo Clinic, percentages of PB blasts $\geq 3\%$ and/or platelet count $< 100 \times 10^9$/L were the only independent predictors of leukemic transformation.[4] In another study from the same institution, presence of unfavorable karyotype [including complex, +8, −7/7q−, −5/5q−, i(17q), inv(3), 12p−, or 11q23] and low platelet count but not the International Prognostic Scoring System (IPSS) score were independent predictors of leukemia-free survival with 5-year leukemia transformation rates of 46% versus 7% for patients with unfavorable and favorable karyotypes, respectively (hazard ratio: 5.5, $P < .0001$).[5] Other investigators, using high-resolution single nucleotide polymorphism (SNP) arrays, have compared chromosomal abnormalities in samples from patients with MPN to those with transformed disease (MPN-BP) and identified an increased number of genomic alterations in the transformed specimens including aberrations of *ETV6* and *TP53* as well as new candidate genes on 7q, 16q, 19p, and 21q.[6]

Similarly, mutations in several genes including *IDH1* and *IDH2*, *TET2*, *RUNX1*, and *TP53* and *SRSF2* have been reported to be involved in the transforming events that contribute to the leukemic transformation in patients with MPNs including PMF.[7-11]

With increasing understanding of the molecular biology of such disease transformation, we are likely to better comprehend the process and potentially identify strategies to prevent or reverse it. The identification of the GR A3669G SNP as a predisposition factor for PMF and its potential collaboration with other molecular events to lead to leukemic transformation is another welcome discovery in study of this lethal disease.

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