Comment on Lu et al, page 771

p53 at the crossroads of MPN treatment

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In this issue of Blood, Lu et al describe the cooperation between an orally bioavailable mouse double minute 2 (MDM2) antagonist (RG7112) and the pegylated interferon α (Peg-IFNα 2a) to target JAK2V617F hematopoietic progenitors and stem cells. Their work provides a rationale for the treatment of patients suffering from myeloproliferative neoplasms (MPNs).1

MPNs are acquired clonal disorders of the hematopoietic stem cells (HSCs) characterized by the hyperplasia of one or several myeloid lineages. Non-BCR-ABL classical MPNs include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). The V617F mutation of the protein kinase JAK2 is the most prevalent genetic abnormality in the 3 types of MPNs (95% in PV and ~50% in ET and PMF). JAK2V617F is a gain-of-function mutation, which leads to constitutive activation of signaling pathways downstream of cytokine receptors.

The discovery of JAK2V617F has rapidly led to the development of JAK2 inhibitors, but the efficiency of the current small molecule inhibitors to reduce the JAK2V617F malignant clone in patients remains disappointing despite major effects on splenomegaly and constitutional symptoms related to inflammation. In contrast, IFNα has been used for >20 years to treat MPN patients including chronic myeloid leukemia patients. It has been shown to efficiently control not only thrombocytosis and erythrocytosis in ET and PV patients but also hematopoiesis by restoring a polyclonal state.2 In contrast to JAK2 inhibitors, the majority of patients treated with IFNα display a partial or complete hematological response associated with a molecular response confirmed by a drop in JAK2V617F allelic burden. Using two Jak2V617F conditional knock-in mouse models, it was reported that IFNα specifically targets Jak2V617F stem cells, yet the mechanisms remain elusive.3,4 Some patients display a long-lasting complete molecular remission even after treatment discontinuation that suggests that IFNα may also impact Jak2V617F stem cells in humans, but further confirmation is needed.

IFNα is also able to stimulate both the transcription of the p53 tumor suppressor via the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway and the subsequent translocation to the nucleus of STAT1/2 and IFN regulatory factor (IRF)-9, which form a heterotrimeric complex triggering activation of the p53 promoter.5 Nevertheless, the basal expression of the MDM2 ubiquitin ligase induces the constant degradation of p53 protein that still remains poised for any stresses. Importantly, JAK2V617F strongly inhibits the stabilization of p53 after induction of DNA damages...
through the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway-dependent increase in MDM2 translation, in cell lines and primary cells from MPN patients. Moreover, the cytokine-independent growth mediated by JAK2V617F in cell lines was inhibited using the inhibitor of MDM2/p53 interaction nutlin-3a, suggesting the important role of the MDM2/p53 axis in JAK2V617F-mediated proliferation.6

Long-term IFNα treatments are usually required to obtain remission but are associated with frequent adverse effects such as fatigue, depression, weight loss, and nausea. Thus, using a drug combination might help lowering the doses or shortening the duration of treatment and appears as a good strategy for successful treatments. Based on previous data, Lu et al developed an original concept to target JAK2V617F malignant cells both by stimulating the p53 transcription via the IFNα and by inhibiting its JAK2V617F-mediated degradation using an MDM2 antagonist (see figure). In their work, they combined low doses of Peg-IFNα with a more potent nutlin derivative than nutlin-3a, called RG7112, which is already used in clinical trials while other second-generation derivatives are also currently tested. Interestingly, the authors make the proof of principle that this strategy is possible. In vitro, they observed an enhancement of progenitor cell death and a preferential targeting of JAK2V617F progenitor cells from PV or MF patients with the drug combination vs Peg-IFNα above, whereas RG7112 alone had no major effect at the dose used. These effects correlated with an increase in p53-target genes and subsequent apoptosis. More importantly, using a xenograft assay in immunodeficient mouse with pretreated CD34+ cells, they found a decreased engraftment after 4 to 7 months and a greater targeting of JAK2V617F cells with the combination compared with either RG7112 or Peg-IFNα alone. These results suggest that the drug combination leads to the preferential targeting of JAK2V617F stem cells. Even if these results are encouraging, it has to be noted that there is a great heterogeneity in the response of patients that could be due to other JAK2V617F-associated mutations (especially in MF patients) or to other mechanisms of resistance that are still not elucidated.7,8

Moreover, this study suggests that the IFNα and MDM2 antagonist act on stem cells through a cell intrinsic mechanism because in vitro the intervention from immunomodulation or from the microenvironment could be excluded. However, these findings have to be further confirmed in vivo because one major interest of IFNα treatment is to target quiescent HSCs by allowing their entry into the cell cycle. To do this, IFNα induces a relaxation of quiescent mechanisms that include a decrease in p53 gene expression that could be compensated by RG7112.9

Altogether, this work further strengthens the role of the p53 axis as an important and druggable pathway in MPNs. This pathway seems to be crucial for the pathologic proliferation of JAK2V617F cells. Indeed, abnormalities in the p53 axis or p53 mutations have been frequently identified (>50%) in post-MPN secondary leukemia compared with other leukemia.10 Altogether, p53 abnormalities might be selected to drive the transformation of MPNs into leukemia. Therefore, the treatment of patients with nutlin derivatives in combination with IFNα might limit the cases of MPN transformation to leukemia. Finally, a similar strategy should also be considered for the treatment of chronic myeloid leukemia because BCR-ABL also up-regulates MDM2, and BCR-ABL-positive stem cells are triggered by IFNα. A main limitation of such an approach may be the thrombocytopenia, which is observed with each single drug treatment, more particularly with MDM2 inhibitors.

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REFERENCES


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Errant innate immune signaling in del(5q) MDS

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In this issue of Blood, Keerthivasan et al have identified that the deletion of mDia1, a chromosome 5q gene, contributes to myelodysplastic syndromes (MDSs) by increasing innate immune signaling in granulocytes.1

Deletion of chromosome 5q (del[5q]) is the most common cytogenetic alteration in MDS. Although minimally deleted regions and common breakpoints have been mapped in del (5q) MDS, all the relevant haploinsufficient genes have not been characterized.2 Adding to the complexity of the del(5q) MDS phenotype, it is becoming apparent that multiple genes

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