Comment on Tiedt et al, page 3931

**JAK2V617F: you can’t have too much**

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In this issue of *Blood*, Tiedt and colleagues use transgenic and retroviral models to demonstrate that the expression level of *JAK2V617F* plays an important role in determining myeloproliferative disease (MPD) phenotype.

The identification of the *JAK2V617F* allele offered significant insight into the pathogenesis of the Philadelphia chromosome-negative MPDs polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Despite this important discovery, many questions remain regarding the molecular basis of PV, ET, and PMF, and the role of the *JAK2V617F* allele in MPD pathogenesis. Most importantly, the mechanism underlying the ability of the identical somatic mutation in *JAK2* to contribute to 3 related, but clinically distinct, disorders remains unknown. Possible explanations for the phenotypic pleiotropy of *JAK2V617F*-positive MPDs include additional somatic mutations, germline modifiers which “instruct” MPD phenotype, and differences in the degree of activation of JAK-STAT signaling by *JAK2V617F* in the different MPDs. Genetic data suggest that gene dosage may play an important role in MPD phenotype, as homozygous *JAK2V617F* mutant erythroid colonies are observed in almost all patients with PV, but only rarely in those with ET.2

These data demonstrate the differences in *JAK2V617F* gene dosage between PV and ET, and suggest that the higher levels of *JAK2* activation associated with *JAK2V617F* homozygosity might result in a PV phenotype, whereas a lesser degree of activation of *JAK2* signaling might result in an ET phenotype.

Previous studies using retroviral bone marrow transplant assays demonstrated that *JAK2V617F* expression can induce marked polycythemia in vivo, but did not allow for an assessment of the effects of varying levels of *JAK2V617F*. Tiedt and colleagues used an alternate approach to address this question, and generated transgenic mice expressing human *JAK2V617F*. Their initial efforts using a constitutive transgene did not result in an MPD phenotype, likely because ubiquitous expression of the *JAK2V617F* transgene has detrimental effects. To circumvent this problem, they developed a conditional transgenic construct that allowed them to direct the expression of the *JAK2V617F* allele to the hematopoietic compartment. Using this approach, they were able to generate mouse lines expressing different levels of *JAK2V617F*, which were associated with distinct MPD phenotypes. In mice that expressed *JAK2V617F* at a level lower than endogenous wild-type *Jak2*, they observed an ET phenotype with marked thrombocytosis, moderate leukocytosis, and an absence of polycythemia. In contrast, mice that expressed the *JAK2V617F* allele at levels similar to wild-type *Jak2* developed a PV phenotype with polycythemia, leukocytosis, and thrombocytosis. Retroviral overexpression of *JAK2V617F* at levels 3-fold higher than wild-type *Jak2* resulted in marked polycythemia without associated thrombocytosis, as has been previously described. Importantly, the level of expression of wild-type and mutated *JAK2* was investigated in patients with the different MPDs; as would be expected, higher expression of *JAK2V617F* was observed relative to wild-type *JAK2* in PV patients, as was lower expression of the mutated allele in ET patient samples.

The authors conclude that the level of expression of *JAK2V617F*, and the ratio of mutant-to-wild-type *JAK2*, contribute significantly to the phenotype of *JAK2V617F*-positive MPDs. Although the data in this paper are consistent with this hypothesis, there remain important questions regarding the role of *JAK2V617F* in the pathogenesis of PV, ET, and PMF. Although the authors were able to generate models of PV and ET by varying the expression of *JAK2V617F*, the role *JAK2* gene dosage plays in signaling and phenotype remains unclear. Do cells homozygous for the *JAK2V617F* allele differ only in the degree of activation of downstream signaling pathways, or are there qualitative differences in signaling between cells homozygous and heterozygous for *JAK2V617F*? Does concomitant expression of wild-type *JAK2* interfere with or modify the ability of *JAK2V617F* to activate signal transduction? Answering these questions will require “knock-in” genetic models in which the *JAK2V617F* allele is introduced into the endogenous *Jak2* locus. In addition, alternate mutations in *JAK2* and in *MPL* are observed only in PV, in the case of *JAK2* exon 12 mutations,3 or in ET/PMF,4,5 in the case of *MPLW515* mutations. Why these mutant alleles are associated with specific clinical phenotypes in contrast to *JAK2V617F* is not known. In addition, given that clinical trials of *JAK2* inhibitors have been initiated in patients with MPDs, it will be important to determine if *JAK2V617F* gene dosage and/or expression level correlate with sensitivity to *JAK2* inhibition.

Overall, the work by Tiedt and colleagues represents a significant advance in our understanding of the molecular pathogenesis of PV, ET, and PMF, and sets the stage for future investigation into how different levels of expression of *JAK2V617F* influence the MPD phenotype.

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

REFERENCES


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