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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 thrombocytopenia (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.

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, or in ET/PMF, 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.

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REFERENCES
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