Polycythemia vera (PV) was first described nearly 120 years ago. In the subsequent century, the clinical syndrome of PV, its natural history, its treatment, and many critical pathogenetic features of the disease were characterized. The discovery of the Janus-associated kinase -2 mutation JAK2 V617F and the characterization of its role in myeloproliferative neoplasms have substantially changed the diagnostic paradigm for PV, and have potential to lead to new therapy and new pathogenetic insights.

Key Words  Polycythemia vera, JAK2, Myeloproliferative neoplasms, Diagnosis
In 2005, Kralovics and colleagues reported the results of an analysis of the Janus-associated kinase 2 (JAK2) gene on chromosome 9 in 244 patients with myeloproliferative neoplasms (128 with PV) [18]. They observed a dominant gain-of-function mutation in which the valine at position 617 was replaced by phenylalanine (V617F) in approximately half the patients. This mutation appeared to confer an in vitro proliferative advantage upon cells into which it was transfected [18].

Over the next five years, studies of JAK2 V617F experienced proliferation as well. Mutations of JAK2 V617F were reported to occur in 80-96% of cases of PV, and to correlate strongly with the 2001 WHO criteria [19-21]. Studies of PV patients lacking JAK2 V617F reported that a significant number of these had mutations in exon 12 of the JAK2 gene resulting in a myeloproliferative phenotype, although there was some suggestion that exon 12 mutations were more likely to be associated with a picture of pure erythrocytosis [22-26]. Unlike the BCR/ABL mutation in chronic myelogenous leukemia, JAK2 V617F is not pathognomonic for PV but is seen in both essential thrombocytosis (ET) and myelofibrosis [18]. It has been reported that JAK2 V617F expression identifies a subset of ET patients who are predisposed to thrombosis and evolution to myelofibrosis (i.e., more like PV patients) [27, 28]. The allele burden of JAK2 V617F mutations has also been proposed as a tool to distinguish ET (low allele burden) from PV (high allele burden).
[29]. The JAK2 V617F allele burden is also associated with response to hydroxyurea, with a high allele burden predicting responsiveness [30], and a reduction in allele burden correlating with clinical response to hydroxyurea [31].

In addition to its role in clinical PV, the identification of JAK2 V617F has had implications for the understanding of the pathogenesis of PV. Transplantation of mice with JAK2 V617F expressing cells leads to a myeloproliferative neoplasm resembling PV [32, 33]. JAK2 V617F appears to be required for the characteristic Epo hypersensitivity of PV erythroid progenitors [34]. However, acquisition of JAK2 mutations does not appear to be the initial molecular event in the pathogenesis of PV, but is rather downstream from some as yet undetermined initiating event [35, 36].

As noted above, JAK2 mutation status can serve as a predictor of response to treatment with hydroxyurea [30], and changes in JAK2 V617F status are associated with response to either hydroxyurea or interferon [31, 37]. Reports of agents targeted to JAK2 in PV are largely limited to studies using various PV model systems [38-40] or to clinical trials in post-PV myelofibrosis [41, 42]. The variable results found in the reported clinical studies may be either agent-specific or specific to the patient subset selected for the study.

As discussed earlier, JAK2 V617F is not pathognomonic of PV but rather is a hallmark of BCR/ABL-negative myeloproliferative neoplasms. Therefore, if it was to be incorporated in a diagnostic schematic analogous to the PVSG criteria, it would be an alternative to M3, which indicates a myeloproliferative neoplasm.

However, the 2008 modification of the WHO diagnostic criteria for PV [43] (Table 3) departed substantially from the underlying concepts of the PVSG criteria. The first major criterion (A1) remains the demonstration of an increased red cell mass, but employs a widely, though not universally [44], accepted criterion based on hemoglobin concentration. The diagnosis of PV is then made by the finding of two additional criteria. This requirement can be met by demonstrating any two of the following: a low serum Epo concentration, a characteristic bone marrow morphology, the presence of EEC, or JAK2 V617F (or a functionally similar mutation, like JAK2 exon 12). This departs substantially from a reliance on readily available clinical and clinical laboratory parameters to more complex testing. PV has become less a clinical diagnosis and more a pathologic and molecular diagnosis.

| Table 3. 2008 World Health Organization criteria for the diagnosis of polycythemia vera. |
|---|
| Major criteria: |
| A1. Hemoglobin > 18.5 g/dL male/16.5 g/dL female; or other evidence of increased red cell mass. |
| A2. Presence of JAK2 V617F or other functionally similar mutation |
| Minor Criteria: |
| B1. Marrow morphology |
| B2. Low serum erythropoietin |
| B3. Bone marrow endogenous erythroid colony formation |
| Marrow morphology: Hyper cellular marrow with trilineage hyperplasia; clustering of pleomorphic megakaryocytes; absent stainable iron: no major inflammatory features. |
| Requirements for diagnosis: |
| A1 + A2 + any one from B |
| A1 + any two from B |
| From [43] |

HOW IS JAK2 V617F USED IN ACTUAL PRACTICE?

JAK2 testing has been suggested as the initial step in the evaluation of erythrocytosis [45]; however, there is no study describing how the general population of hematologists uses this test which could be compared to the report by Strieff et al. in 2002, which describes the diagnostic and management practices prevalent in the early post-PVSG era [46]. In a recent report, the use of JAK2 V617F in a single academic practice was described [47]. Patients newly presenting with a diagnosis of PV were routinely tested for the mutation. Of established patients, patients who did not meet the 2001 WHO diagnostic criteria fully tended to be more likely to be tested for JAK2 V617F mutation; patients who seemed to have a clearly established diagnosis.

CONCLUSION

The discovery of the JAK2 V617F mutation, the definition of its frequency in PV and other myeloproliferative neoplasms, and the identification of its pathophysiologic implications, have transformed the diagnostic approach to PV from one based in the clinic and clinical laboratory to a truly molecular paradigm. JAK2 V617F has the potential to guide therapy of PV and other BCR/ABL-negative myeloproliferative neoplasms, whether as a therapeutic target or as a marker of response to therapy or of progression risk.

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