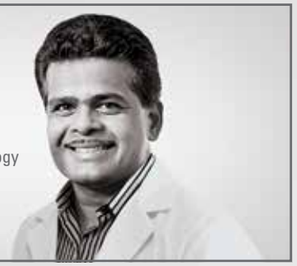
What is the significance of the *JAK2*V617F mutation in myelofibrosis?

Kris Vaddi, DVM, PhD
Group Vice President,
Pharmacology and Toxicology
Incyte Corporation



An enlightening breakthrough and its clinical impact

The discovery of *JAK2*V617F was a significant breakthrough that markedly transformed our knowledge about the Janus kinase (JAK) pathway in myeloproliferative neoplasms (MPNs), including myelofibrosis.[1] The intensive research inspired by this discovery continues today and is adding to our understanding of myelofibrosis and other MPNs.

As important as this discovery may be, the *JAK2*V617F mutation status of a myelofibrosis patient may have limited clinical impact. Mutation status may be relevant in the diagnosis of myelofibrosis, but for clinical decisions it appears to have limited value.[2,3]

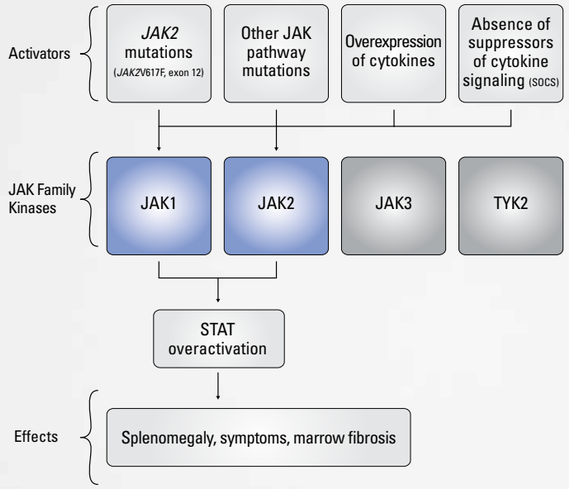
Overactive JAK pathway is the hallmark of myelofibrosis

The discovery of the *JAK2*V617F mutation spurred further research into the JAK pathway, which plays a key role in hematopoiesis and immune function.[1,4] The JAKs comprise a family of 4 cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3 and TYK2.[4] Proinflammatory cytokines signal primarily through JAK1, whereas hematopoietic growth factors, such as erythropoietin and thrombopoietin, signal primarily through JAK2. Activation of the JAK pathway triggers STATs (signal transducers and activators of transcription) to regulate normal inflammatory responses and hematopoiesis.[4]

The *JAK2*V617F mutation is just one way the JAK pathway can become persistently activated in myelofibrosis. Researchers originally thought that the *JAK2*V617F mutation in MPNs was analogous to *BCR-ABL* in CML, in that it is the sole driver of disease.[1,5]

Contrary to initial scientific hypotheses, the presence of the *JAK2*V617F mutation did not explain all the cases and clinical manifestations of myelofibrosis and related MPNs.[5] In addition to *JAK2*V617F, a number of mechanisms (see Figure below) were identified to cause overactivation of the JAK pathway. Myelofibrosis is a complex disease characterized by multiple genetic, epigenetic and cellular alterations. Most importantly, overactive JAK signaling, and not *JAK2*V617F, is the hallmark of myelofibrosis.

The *JAK2*V617F mutation represents only one way that the JAK pathway can be defective[4-6]



STAT phosphorylation via JAK1 and JAK2 signaling can become overactivated via excess cytokines, *JAK2* mutations, decreased SOCS and other abnormalities of pathway components.

Myelofibrosis diagnosis and prognosis without the mutation

Because myelofibrosis is not mutation specific, no particular clonal marker—including *JAK2*V617F—is necessary for the diagnosis.[2] Myelofibrosis can be diagnosed in places or circumstances where genetic testing is not possible by applying the WHO criteria properly.

Incidence of *JAK2*V617F mutation in MPNs[1,5]

Myelofibrosis	~50%
Polycythemia vera	97%
Essential thrombocythemia	~50%

*JAK2*V617F mutation status was not demonstrated to be either predictive or prognostic in myelofibrosis in a study of the factors that might cause a shorter life expectancy.[7]

Regardless of the pathogenesis of a given myelofibrosis patient's symptoms and splenomegaly, the JAK pathway is overactive. Knowing the exact reason for a particular patient's overactive JAK pathway appears to have limited clinical value currently.

The JAK2 component of the pathway is not the whole story

Another common feature of myelofibrosis is excess circulating inflammatory cytokines, which are thought to mediate many symptoms associated with the disease, especially the constitutional symptoms. Cytokines signal through multiple components of the JAK pathway, including JAK2 and other members of the JAK family, but more prominently through JAK1.[4]

Furthermore, the inverse relationship between the presence of constitutional symptoms and survival implicates the JAK pathway as a key driver of disease.[7]

Role of *JAK2*V617F mutation status in myelofibrosis

The discovery of the *JAK2*V617F mutation has greatly advanced the understanding of the pathogenesis of MPNs, but the clinical utility of mutation status remains unclear in myelofibrosis.

The JAK pathway, rather than the *JAK2*V617F mutation, is important for the pathogenesis of myelofibrosis, suggesting that mutational status alone should not dictate clinical strategies and approaches for patients with myelofibrosis.

Myelofibrosis has been shown to be not a mutation-specific disease, but a pathway-specific disease.

To learn more visit www.JAK2V617FnegativeMF.com

BCR-ABL = breakpoint cluster region-Abelson leukemia virus oncogene; CML = chronic myelogenous leukemia; TYK2 = tyrosine kinase 2; WHO = World Health Organization.

References: 1. Vainchenker W, Constantinescu SN. *Hematology.* 2005:195-200. **2.** Vardiman JW, Thiele J, Arber DA, et al. *Blood.* 2009;114:937-951. **3.** Verstovsek S, Kantarjian H, Mesa RA, et al. *N Engl J Med.* 2010;363:1117-1127. **4.** Quintás-Cardama A, Vaddi K, Liu P, et al. *Blood.* 2010;115:3109-3117. **5.** Vainchenker W, Delhommeau F, Constantinescu SN, Bernard OA. *Blood.* 2011;118:1723-1735. **6.** Fourouclas N, Li J, Gilby DC, et al. *Haematologica.* 2008;93:1635-1644. **7.** Cervantes F, Dupriez B, Pereira A, et al. *Blood.* 2009;113:2895-2901.