

The *JAK2* V617F revolution in myeloproliferative neoplasms

Ayalew Tefferi

Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN, USA
E-mail: tefferi.ayalew@mayo.edu

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TITLE	A unique clonal <i>JAK2</i> mutation leading to constitutive signalling causes polycythemia vera.
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In 1951, William Dameshek (1900-1969) penned an editorial in *Blood* highlighting shared phenotype (i.e., trilineage proliferation, splenomegaly, bone marrow fibrosis) among the myeloproliferative and related myeloid neoplasms, including chronic myeloid leukemia (CML; then referred to as “chronic granulocytic leukemia”), polycythemia vera (PV), essential thrombocythemia (ET; then referred to as “megakaryocytic leukemia”), and primary myelofibrosis (PMF; then referred to as “idiopathic or agnogenic myeloid metaplasia of spleen”).¹ He also discussed transitional (e.g., post-PV myelofibrosis) and pre-fibrotic states and contended that these “myeloproliferative disorders” were closely interrelated and represented variable manifestations of a constitutively-driven bone marrow proliferative activity arising from a “hitherto undiscovered stimulus”¹

In 1960, Nowell and Hungerford described the Philadelphia chromosome that ultimately led to the identification of *BCR::ABL1* as the disease-causing mutation in CML and the successful launching of imatinib (ABL tyrosine kinase inhibitor) as a disease-modifying drug therapy. By contrast, the molecular basis of PV, ET, and PMF remained elusive until the March, 2005 breakthrough communication by James *et al.*, describing a novel Janus kinase 2 JAK/STAT activating mutation (*JAK2*V617F located in the auto-inhibitory JH2 pseudo-kinase domain - a G to T somatic mutation at nucleotide 1849, in exon 14, resulting in the substitution of valine to phenylalanine at codon 617) in PV, ET and PMF (discovery patent filing in October 2004).² The authors utilized short interfering RNA to knock down *JAK2* expression and demonstrated the essential role of *JAK2* in erythropoietin-independent growth in PV (Figure 1). *JAK2* mutation screening led to the detection of *JAK2*V617F in two of three

patients with PV and neither of two control subjects and subsequently in 40 of 45 patients with PV but in none of 15 control subjects or 35 patients with secondary erythrocytosis. The somatic origin of the mutation was confirmed by its presence in granulocytes, erythroblasts, and platelets but not T cells. Additional *in vitro* and *in vivo* studies revealed that the mutation induced both cytokine independence and hypersensitivity, erythropoietin-independent STAT activation, and erythrocytosis in mouse transplant models. The presence of only the mutated clone in a substantial fraction of patients with PV suggested chromosome 9p loss of heterozygosity, resulting from mutant allele duplication by mitotic recombination. Finally, consistent with Dameshek’s speculations, *JAK2*V617F was also detected in nine of 21 patients with ET and three of seven with PMF.

The observations by James *et al.* were also independently described by three other groups using different methodologies and together led to the subsequent discovery of other JAK/STAT activating mutations, including *JAK2* exon 12, *CALR* and *MPL*.³ The impact of the *JAK2*V617F discovery on clinical practice has been substantial, although not to the same extent as that of *BCR::ABL1*. *JAK2*, *CALR*, and *MPL* mutations are now included in formal classification and diagnostic criteria and variably used as prognostic markers and therapeutic targets. In the latter regard, although *JAK2*- and *CALR*-targeted therapies have been successful in effective palliation of symptoms, they have so far fallen short in terms of selective and durable suppression of the disease clone.

Disclosures
No conflicts of interest to disclose.

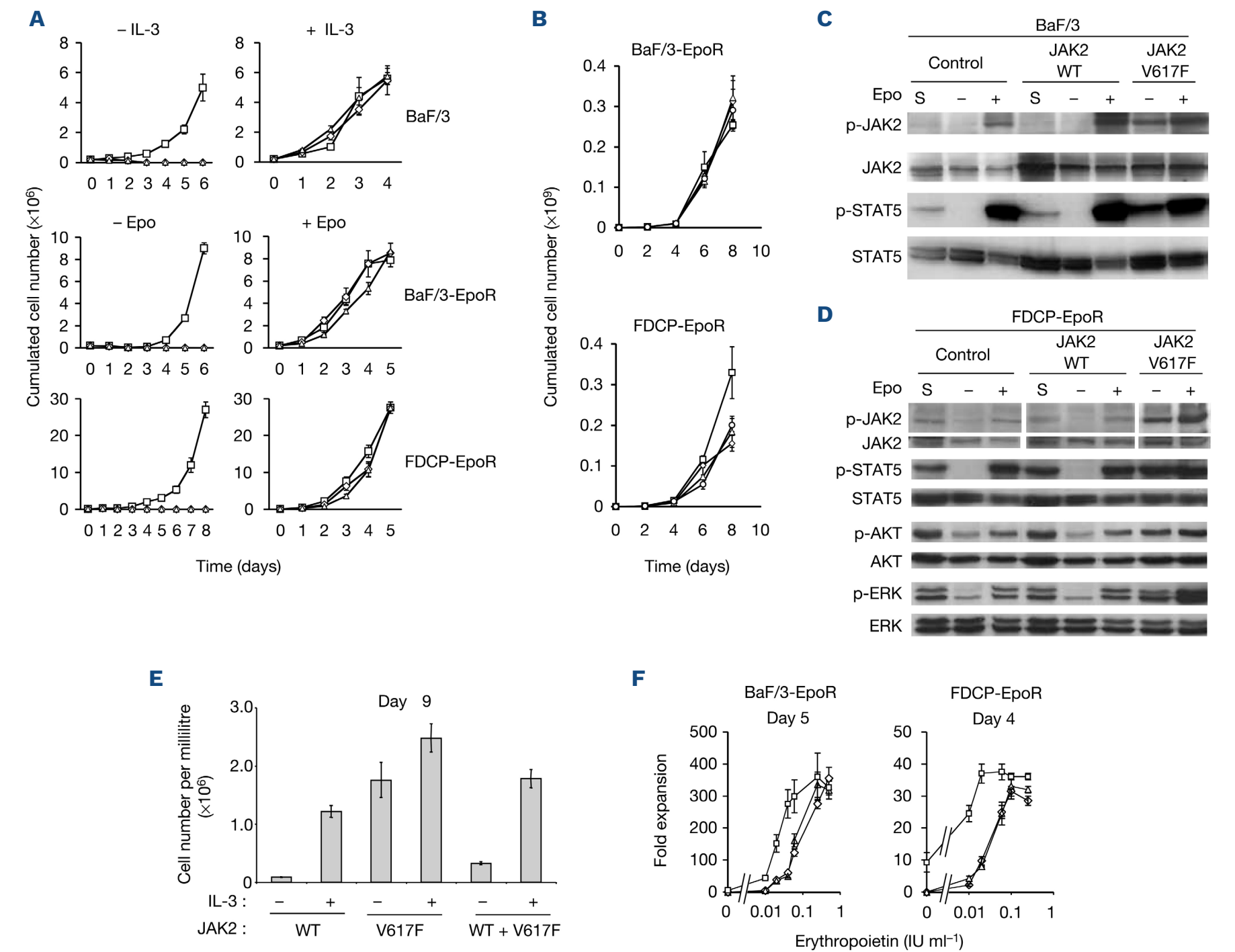


Figure 1. Mutated JAK2 induces constitutive signaling leading to growth factor independence. (A) Short-term growth of BaF/3, BaF/3-EpoR and FDCP-EpoR cells. Cells were sorted according to a similar level of green fluorescence protein after retroviral transduction and cultured in the presence or absence of cytokine. Results for V617F JAK2 mutant cells are represented by open squares, those for wild-type JAK2 cells by open triangles, and those transduced with control retrovirus by open diamonds. (B) Long-term growth of the V617F JAK2 BaF/3-EpoR and FDCP-EpoR cells selected for growth-factor independence. V617F JAK2 mutant cells without erythropoietin (open circles), with erythropoietin (open squares), wild-type JAK2 cells with erythropoietin (open triangles) and control retrovirus cells with erythropoietin (open diamonds) are shown. (C) Studies of JAK2 and STAT5 phosphorylation by western blotting in wild-type BaF/3 cells, Baf/3 cells overexpressing wild-type JAK2 or mutated JAK2 cells (autonomous for growth). S: steady state. The minus sign indicates 12 hours after interleukin-3 deprivation, whereas the plus sign indicates after 100 ng/mL interleukin-3 re-stimulation. (D) Studies of JAK2, STAT5, ERK and AKT phosphorylation by western blotting in wild-type FDCP-EpoR cells, FDCP-EpoR cells overexpressing wild-type JAK2 or mutated JAK2 cells (autonomous for growth). The minus sign indicates 12 hours after erythropoietin deprivation, whereas the plus sign indicates 10 IU/mL erythropoietin re-stimulation. (E) Co-expression of wild-type JAK2 inhibits the autonomous growth of BaF/3 cells (cell counts of three replicates $\pm$ standard deviation) induced by the V617F JAK2 mutant. (F) Expression of the V617F JAK2 mutant (open squares) but not of wild-type JAK2 (open triangles) or an empty retrovirus (open diamonds) induces erythropoietin hypersensitivity in BaF/3-EpoR and FDCP-EpoR cells. Error bars in (A), (B), and (F) indicate the standard error of mean. Epo: erythropoietin; EpoR: erythropoietin receptor; IL-3: interleukin-3; WT: wild-type; Figure reproduced, with permission, from James C, *et al.*²

References

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