

COMMENTARY

JAK the triggerFrançois-Xavier Mahon^{*1}¹Laboratoire d'hématopoïèse leucémique et cible thérapeutique, Université Victor Segalen Bordeaux 2, Service des maladies du sang CHU de Bordeaux, INSERM E0217, 146 rue Léo Saignat, Boite 50, 33076 Bordeaux Cedex, France

A somatic mutation that leads to activation of the JAK2 tyrosine kinase has recently been identified as a recurrent genetic abnormality in several different myeloproliferative disorders. A translocation generating the constitutively activated fusion protein PCM1-JAK2 has also been recently found in atypical chronic myelogenous leukemia and acute leukemia. This recent spate of independent studies (one of which is published in this issue of Oncogene) establish abnormal JAK2 activation as the underlying defect in a significant number of cases of myeloproliferative disease, and JAK2 as an important new therapeutic target.

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A number of diseases including cancer are linked to dysregulation of tyrosine kinases. More than 500 proteins with kinase activity are coded by the human genome, but only 90 or so are tyrosine kinases. Exchange of phosphate between different substrates is the intracellular mode to communicate. This molecular language is precisely regulated by protein kinases or phosphatases. However, these enzymes may be dysregulated and activated in cancer cells leading to a loss of normal cell growth control.

The hematopoietic cytokine receptors receive growth signals from outside the cell and transduce these via their cytoplasmic tails by activating members of the Janus kinase (JAK) family of tyrosine kinase proteins, which phosphorylate cytoplasmic targets. JAK2 is one member of this family and is critical to the signalling of many hematopoietic cytokine and growth factor receptors (Ihle, 1995). A number of recent studies now implicate the dysregulation of this kinase in the development of myeloproliferative disease.

The myeloproliferative disorders include chronic myelogenous leukaemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and idiopathic myelofibrosis (IM). For each of these disorders, a particular lineage of myeloid cell is involved and present in excessive numbers in the peripheral blood, that is,

granulocytic for CML, erythroid for PV or platelet for ET, while marrow fibrosis predominates in the IM. To these myeloproliferative disorders may also be added hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD), chronic myelomonocytic leukemia and atypical CML (aCML). Among all of these diseases, CML is a model because a marker, the Philadelphia chromosome, makes it possible to recognize the abnormal cells and thus to identify its molecular counterpart the *BCR-ABL* gene. BCR-ABL protein exhibits a constitutive tyrosine kinase activity, which drives leukemic proliferation and preferentially myeloid cell expansion. Outstanding work regarding the understanding of BCR-ABL and its dysregulated kinase has led to focusing research on the protein kinases and their essential role in leukemogenesis. This effort has been underpinned by the discovery of imatinib, which inhibits the kinase activity of BCR-ABL. This is the first tyrosine kinase inhibitor developed for clinical application, and has proved highly successful in CML (Druker *et al.*, 2001).

In the current issue of *Oncogene*, Bousquet *et al.* (2005) contribute to a new body of evidence that points to the importance of a different protein tyrosine kinase, JAK2, in myeloproliferative disease. They report two cases of atypical chronic myeloid leukemia (aCML) with a t(8;9)(p22p24) translocation and a molecular rearrangement PCM1-JAK2. Seven other cases with PCM1-JAK2 fusion (aCML ($n=5$) and acute leukemia ($n=2$)) were also reported very recently by the group headed by Nick Cross (Reiter *et al.*, 2005). In the PCM1-JAK2 fusion, a constitutive activation of the kinase is a consequence of homodimerization mediated by the coiled-coil domains of PCM1, which brings together the linked JAK2 domains (Lacronique *et al.*, 1997). The mechanism has already been reported for activation of the ABL kinase by BCR or TEL and PDGFR.

At the same time, several teams have discovered and now report a single somatic mutation in the JAK2 gene that appears responsible for several different myeloproliferative disorders (Baxter *et al.*, 2005; James *et al.*, 2005; Kralovics *et al.*, 2005; Levine *et al.*, 2005). This mutation, which appears to be acquired somatically in hematopoietic stem cells, is found in most patients with PV and in roughly one-third of patients with ET or IM. Functional analysis demonstrates that the mutation, a valine to phenylalanine substitution at codon 617 (Val617Phe), confers cytokine-independent growth *in vitro*, deregulates signalling pathways down-

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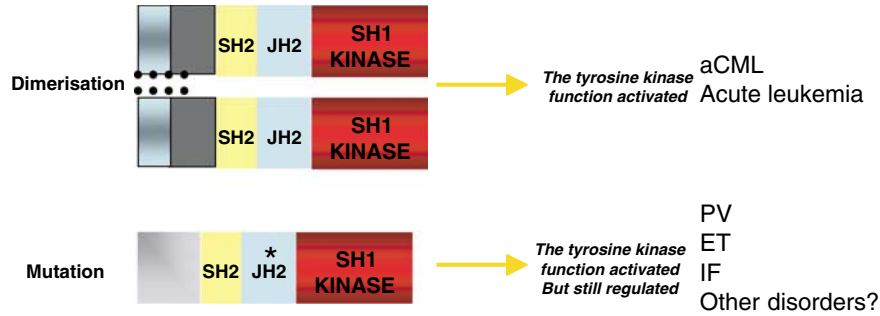


Figure 1 Activation of JAK2 kinase in leukaemia and myeloproliferative disorders.

stream of JAK2, and causes proliferation in a murine model.

According to the predicted structure of JAK2, the Val617Phe mutation occurs in the pseudo-kinase domain known as the JH2 domain, and would be expected to disrupt its interaction leading to the loss of JH2 domain inhibition. Thus, the discovery of this mutation reveals an alternative mechanism of constitutive JAK-2 kinase activation. Fused to a 'dimerizing' protein such as PCM1 or TEL, the activation of JAK2 is probably stronger than that which occurs as a consequence of the mutation Val617Phe, leading to diseases such as acute

leukemia or aCML, which are more aggressive than PV, ET or IM (Figure 1).

If one combines the currently reported incidence of the Val617Phe mutation and activating JAK2 translocations, JAK2 activation has now superseded BCR-ABL as the most frequent known abnormality in myeloproliferative disorders. This suggests that JAK is not 'just another kinase'. Rather, JAK-2 kinase activation would seem to be the triggering factor of an important group of hematological diseases, thereby suggesting that it could be a very good therapeutic target for as yet undiscovered tyrosine kinase inhibitors.

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