JAK2 mutations in myeloproliferative neoplasms

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Introduction

Myeloproliferative neoplasms (MPN) are clonal disorders of hematopoietic stem cells that clinically manifest as overproduction of cells that contribute to the myeloid lineage. These include the "classical MPN's" chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocytopenia (ET) and primary myelofibrosis (PMF) (Vardiman et al., 2002), as well as "atypical MPN's"; chronic eosinophilic leukemia (James et al., 2005), chronic myelomonocytic leukemia (CMML), and systemic mastocytosis (SM) (Tefferi and Gilliland, 2006).

In 1951, CML, PV, ET and PMF were recognized to have significant overlap in both clinical and biological features and were felt to be related diseases (Dameshek, 1951). In 1960, CML was recognized as a distinct entity after discovery of the Philadelphia chromosome (Nowell and Hungerford, 1960).

In the early 1980s, Fialkow analyzed X chromosome inactivation patterns in women with PV, ET, PMF or CML carrying a polymorphic variant of the gene for glucose-6-phosphate dehydrogenase. Based on the observations, they established that all four diseases were clonal stem cell disorders (Adamson et al., 1976; Fialkow et al., 1977; Fialkow et al., 1981). Recently in 2005, several independent groups identified a somatic mutation involving a protein tyrosine kinase in patients with PV, ET and PMF (Baxter et al., 2005; James et al., 2005; Kralovics et al., 2005; Levine et al., 2005). This was a JAK2 point mutation at codon 617, subsequently named JAK2V617F which results from a G --> T transversion at nucleotide 1849 in exon 14 of the JAK2 gene, the consequence of which is substitution of valine by phenylalanine at codon 617. The mutation is present in hematopoietic cells from affected individuals, but not in the germline, suggesting that this mutation is acquired as a somatic disease allele in the hematopoietic compartment. This mutation is observed in 95% of patients with PV, and 50% of patients with ET and PMF (Tefferi and Gilliland, 2005). In the last 2 years, additional JAK2 mutations have been reported and have shown to induce PV-(JAK2)-like phenotype in mice (Scott et al., 2007b).

JAK structure and function

The acronym JAK stands for Just Another Kinase, which refers to the discovery of multiple tyrosine kinase family members. Janus kinases (JAKs) are named after the Roman god with two faces because they contain two symmetrical kinase-like domains; the C-terminal JAK homology 1 (JH1) and the immediately adjacent JH2 or pseudokinase domain (Saharinen and Silvennoinen, 2002; Feener et al., 2004). Valine 617 is within the JH2 domain. There are four mammalian members of the JAK family of receptor-associated tyrosine kinases: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). They comprise of seven homologous JH domains organized into four regions; kinase (JH1), pseudo-kinase (JH2), FERM (the N-terminal JH7, JH6, JH5 and part of JH4) and SH2-like (JH3 and part of JH4).
The carboxy-terminal portion of these molecules includes a distinctive kinase domain (JH1) which is catalytically active and a catalytically inactive pseudo kinase domain (JH2) which is felt to regulate the activity of JH1. The amino-terminal JH domains, JH3-JH7, constitute a FERM (four-point-one, ezrin, radixin, moesin) domain and mediate association with receptors (Funakoshi-Tago et al., 2006). In humans, JAK1 is located on chromosome 1p31.3, JAK2 on 9p24, JAK3 on 19p13.1 and TYK2 on 19p13.2. Each one of these genes ranges in size from 120 to 130 kDa containing 20 - 25 exons. Expression is ubiquitous for JAK1, JAK2 and TYK2 but restricted to hematopoietic cells for JAK3.

Typically, JAK kinases function through their interaction with cytokine receptors that lack intrinsic kinase activity. Ligand binding (e.g. erythropoietin, thrombopoietin) to the appropriate cytokine receptor (type 1 or type 2 cytokine receptors; e.g. EpoR, MPL) results in juxtaposition of JAKs followed by JAK kinase phosphorylation and activation, cytokine receptor phosphorylation and creates a docking site for the recruitment and activation of signal transducers and activators of transcription (STATs) (Mertens and Darnell, 2007). Following phosphorylation, activated STATs dimerize and translocate into the nucleus to induce target gene transcription. This entire process is tightly regulated at multiple levels by protein tyrosine phosphatases, suppressors of cytokine signaling (SOCS) and protein inhibitors of activated STAT (Starr and Hilton, 1999; Sasaki et al., 2000; Stofega et al., 2000).

JAK2 was first identified in 1993 (Harpur et al., 1992) and was found to be an essential mediator for erythropoietin signaling (Withuhn et al., 1993). The JAK2 gene is located on chromosome 9p24. Genetic deletion of JAK2 results in embryonic death due to lack of definitive erythropoiesis, and JAK2-deficient hematopoietic progenitors do not respond to erythropoietin stimulation, suggesting that JAK2 is the only JAK kinase responsible for erythropoietin receptor signaling (Parganas et al., 1998).

**JAK2V617F mutations in PV, ET and PMF**

In 2005, several independent groups identified a recurrent mutation in the JAK2 tyrosine kinase in most patients with PV, ET or PMF (Baxter et al., 2005; James et al., 2005; Kralovics et al., 2005; Levine et al., 2005). Subsequently, the mutation was also described in other myeloid neoplasms (Steensma et al., 2005). JAK2V617F is an exon 14 G to T somatic mutation. This mutation is a guanine-to-thymidine substitution, which results in a substitution of valine for phenylalanine at codon 617 within the JH2 domain of JAK2 (JAK2V617F). The JH2 domain is believed to be auto-inhibitory (Saharinen and Silvennoinen, 2002), and valine 617 plays an important role in JAK2 kinase auto-inhibition (Lindauer et al., 2001). Thus, the valine to phenylalanine substitution at codon 617 results in constitutive kinase activity resulting in a gain-of-function mutation (Ihle and Gilliland, 2007). Studies have shown that expression of JAK2V617F results in transformation of Ba/F3 cells to IL-3 independent growth, unlike wild-type JAK2 (James et al., 2005). Similarly, coexpression of JAK2V617F and erythropoietin receptor, thrombopoietin receptor (MPL), or granulocyte-macrophage colony stimulating factor (GM-CSF) receptor (all homodimeric Type 1 cytokine receptors) result in cytokine independent growth and activation of signal transduction (Lu et al., 2005). In addition, expression of JAK2V617F results in constitutive activation of downstream signaling pathways including the JAK-STAT, PI3K/AKT and MAPK/ERK pathways (James et al., 2005; Kralovics et al., 2005; Levine et al., 2005).

The JAK2V617F mutation has been reported in over 95% of patients with PV, 50% of patients with ET or PMF, 20% in certain other MPNs including refractory anemia with ring sideroblasts and thrombocytosis (RARS-T), and less than 5% in AML or MDS (Renneville et al., 2006; Steensma et al., 2006; Verstovsek et al., 2006). JAK2V617F is a somatically acquired mutation and a subset of patients with PV are homozygous for the JAK2V617F allele as a result of mitotic recombination and duplication of the mutant allele, known as uniparental disomy. Uniparental disomy of chromosomal locus 9p24, including JAK2, had previously been noted in PV (Kralovics et al., 2002), and later the JAK2V617F allele was identified through analysis of the minimal region of uniparental disomy (Kralovics et al., 2005). It has been shown that most patients with PV possess JAK2V617F homozygous mutant erythroid progenitors, while most patients with ET possess only heterozygous and wild-type erythroid colonies (Scott et al., 2006). These observations suggest that mitotic recombination and JAK2V617F homozygosity is an early genetic event in the development of PV, but not ET.

In humans, JAK2V617F mutation occurs at the stem cell level and is present in hematopoietic stem cell progenitors (Baxter et al., 2005; Jamieson et al., 2006). It is believed to be myeloid lineage specific.
because it is present in erythroid and granulocyte-macrophage progenitors (Baxter et al., 2005; James et al., 2005). However, some reports have suggested JAK2V617F clonal involvement of B (Ishii et al., 2006), T (Ishii et al., 2006), and NK (Bellanne-Chantelot et al., 2006) lymphocytes. These observations confirm the stem cell nature of JAK2V617F MPN's.

In retroviral transplant mouse models JAK2V617F induces a PV-like phenotype: erythrocytosis, low serum erythropoietin level, splenomegaly due to extramedullary hematopoiesis, leukocytosis, megakaryocytic hyperplasia and ultimately evolution to myelofibrosis (Lacout et al., 2006; Wernig et al., 2006). It has also been shown that in JAK2V617F transgenic mice, manipulation of mutant gene expression results in either an ET (lower expression compared with wild-type allele) or PV phenotype with (equal expression) or without (higher expression) thrombocytosis (Tiedt et al., 2008). Based on the above experiments, we observe that mutant allele burden in patients with ET is significantly lower than that seen in patients with either PV or PMF (Kittur et al., 2007; (Tefferi et al., 2007; Vannucchi et al., 2007b; Tefferi et al., 2008). In PV, a higher allele burden is the result of JAK2V617F homozygosity. Although JAK2V617F is central to the pathogenesis of PV, ET, PMF, the presence of the same allele in three clinically distinct MPN's suggests that there might be additional inherited or acquired genetic predisposition. A familial tendency has been reported in 72 families with at least two members with MPN's that were tested for JAK2V617F (Bellanne-Chantelot et al., 2006). The presence of JAK2V617F in these families ranged from some families in which all members carried the mutation, to some in which none of the members with MPN had the JAK2V617F mutation. This pattern is consistent with a two-hit hypothesis, with an inherited genetic predisposition to MPN (Pardanani et al., 2006a).

There is further evidence to suggest that other somatic alleles are involved along with JAK2V617F in the development of MPN's. It is noted that in a subset of JAK2V617F positive MPN who transform to AML, the leukemic blasts are JAK2V617F mutation negative (Theocharides et al., 2007).

Other reported JAK2 exon 14 mutations include D620E (PV, MPN, unclassifiable), E627E (MPN, unclassifiable), C616Y (PV), V617F from c.1848_1849delinsCT (post-ET MF) and V617F/C618R from c.1849 - 1852GTCT > TTTC (PV) (Grunebach et al., 2006; Schnittger et al., 2006; Wong et al., 2007; Zhang et al., 2007).

**JAK2 exon 12 mutations**

A small proportion of patients with PV are JAK2V617F negative when tested by sensitive allele-specific assays (Jones et al., 2005). However, in 2007, Scott and colleagues identified a set of JAK2 exon 12 mutations in JAK2V617F-negative patients with PV (Scott et al., 2007b). The majority of these cases were found to harbor 1 of 4 exon 12 JAK2 mutant alleles: N542-E543del, F537-K539delinsL, a point mutation that results in substitution of lysine for leucine at codon 539 (K539L), and H538QK539L. All four exon 12 mutant alleles induced cytokine-independent/hypersensitive proliferation in erythropoietin receptor-expressing cell lines and constitutive activation of JAK-STAT signalling (Scott et al., 2007b). In addition, JAK2K539L induced a PV phenotype in a murine transplant model. Unlike JAK2V617F, JAK2 exon 12 mutations are only observed in JAK2V617F- negative PV (i.e. approximately 5% of all PV cases) (Scott et al., 2007a; Butcher et al., 2008), and are specific to patients with isolated erythrocytosis without concomitant leukocytosis or thrombocytosis.

Several other exon 12 mutation variants have been identified; R541 - E543delinsK, I540 - E543delinsMK, V536-I546dup11, F537-I546dup10 + 547L and E543-D544del (Percy et al., 2007; Butcher et al., 2008; Pietra et al., 2008).

**MPL mutations**

Approximately 50% of ET and PMF patients are JAK2V617F negative. This led Pikman and colleagues (Pikman et al., 2006) to study whether other genes in the JAK-STAT signaling pathway might be mutated in JAK2V617F negative ET and PMF. This led to the identification of mutations of the thrombopoietin receptor (MPL), which substitute either leucine or lysine by tryptophan at codon 515. These mutations occur in 10% of JAK2V617F negative PMF and in 2% of JAK2V617F negative ET, but not observed in PV or other myeloid malignancies (Pardanani et al., 2006b).
Clinical correlates of JAK2 mutations in PV, ET and PMF

The prognostic significance of the JAK2V617F mutation has not been precisely delineated. In ET, the presence of JAK2V617F has been associated with advanced age, higher hemoglobin level, higher leukocyte counts and lower platelet counts (Antonioli et al., 2005; Campbell et al., 2005; Wolanskyj et al., 2005; Kittur et al., 2007). In addition in mutation-positive patients with ET, JAK2V617F allele burden has been directly correlated with leukocyte count, platelet count and the presence of palpable splenomegaly (Kittur et al., 2007; Vannucchi et al., 2007b). Although JAK2V617F mutant and wild-type patients differ in regards to laboratory parameters and clinical features, there were no differences in overall survival, or myelofibrotic and leukemic transformations. In PV, JAK2V617F homozygous patients were noted to have a higher hemoglobin level, higher leukocyte count, lower platelet count, and an increased incidence of pruritus but not an increased risk of thrombosis (Vannucchi et al., 2007b). A similar set of correlations were made for higher mutant allele burden in PV, measured by quantitative assays (Tefferi et al., 2007; Vannucchi et al., 2007a). In PMF, the presence of JAK2V617F was associated with older age at diagnosis, higher leukocyte count and presence of pruritus (Tefferi et al., 2005). Furthermore, JAK2V617F “homozygous” PMF patients displayed even higher leukocyte count and spleen size (Barosi et al., 2007). In PMF, the presence of the JAK2V617F mutation is associated with poorer overall survival (Campbell et al., 2006). However, these data suggest that JAK2V617F mutational status may have prognostic significance in PV, ET and PMF, but additional studies of large patient cohorts are needed to confirm these findings.

The prevalence of JAK2 exon 12 is too low to enable accurate assessment of prognostic impact. Nevertheless, JAK2 exon 12 mutations have been associated with a PV phenotype that is more likely to present with isolated erythrocytosis (Scott et al., 2007b; Pietra et al., 2008).

Conclusion

The discovery of the JAK2V617F mutation in 2005 has been pivotal to our understanding of the pathogenesis of PV, ET and PMF. The subsequent discovery in 2007 of the JAK2 exon 12 mutations in JAK2V617F negative PV suggests that activation of the JAK-STAT pathway is important in the pathogenesis of JAK2V617F-negative MPN. Understanding the molecular pathogenesis of diseases, such as bcr-abl in CML, and now JAK2V617F in PV, ET, and PMF has led to the development of small molecule inhibitors of JAK2.

Accordingly, a number of anti-JAK2 small molecule drugs have been tested in preclinical models and some have been introduced into clinical trials (Pardanani et al., 2007; Lashe et al., 2008; Pardanani, 2008). Preliminary results from currently ongoing JAK2 inhibitor drug trials (INCB018424, XL019) suggest remarkable activity in alleviating symptomatic splenomegaly and constitutional symptoms in patients with primary or post-PV/ET myelofibrosis (Verstovsek, 2007a; Verstovsek, 2007b). Despite the discovery of JAK2 and MPL mutations there are several unanswered questions regarding the etiology of PV, ET and PMF; how does a single disease allele contribute to three distinct clinical disorders? Will JAK2 inhibitor therapy offer clinical benefit to patients with PV, ET and PMF?

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