Myeloproliferative Neoplasms: JAK2 Signaling Pathway as a Central Target for Therapy

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Abstract

The discovery of the *JAK2*V617F mutation followed by the discovery of other genetic abnormalities allowed important progress in the understanding of the pathogenesis and management of myeloproliferative neoplasms (MPN)s. Classical Breakpoint cluster region-Abelson (*BCR-ABL*)−negative neoplasms include 3 main disorders: essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). Genomic studies have shown that these disorders are more heterogeneous than previously thought with 3 main entities corresponding to different gene mutations: the JAK2 disorder, essentially due to JAK2V617F mutation, which includes nearly all PVs and a majority of ETs and PMFs with a continuum between these diseases and the myeloproliferative leukemia (MPL) and calreticulin (CALR) disorders, which include a fraction of ET and PMF. All of these mutations lead to a JAK2 constitutive activation. Murine models either with JAK2V617F or MPLW515L, but also with JAK2 or MPL germ line mutations found in hereditary thrombocytosis, have demonstrated that they are drivers of myeloproliferation. However, the myeloproliferative driver mutation is still unknown in approximately 15% of ET and PMF, but appears to also target the JAK/Signal Transducer and Activator of Transcription (STAT) pathway. However, other mutations in genes involved in epigenetics or splicing also can be present and can predate or follow mutations in signaling. They are involved either in clonal dominance or in phenotypic changes, more particularly in PMF. They can be associated with leukemic progression and might have an important prognostic value such as additional sex comb-like 1 mutations. Despite this heterogeneity, it is tempting to target JAK2 and its signaling for therapy. However in PMF, Adenosine Tri-Phosphate (ATP)-competitive JAK2 inhibitors have shown their interest, but also their important limitations. Thus, other approaches are required, which are discussed in this review.

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Introduction

Myeloproliferative neoplasms (MPN) are clonal hematopoietic disorders characterized by an increased number of mature myeloid peripheral blood cells.[1] The World Health Organization classification distinguishes 3 classical Philadelphia-negative MPN: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Until 2005 and the discovery of a somatic point mutation in Janus-Activated Kinase 2 (JAK2) tyrosine kinase (JAK2V617F), the genomic landscape of MPN was unknown. Based on the hypothesis that JAK/STAT signaling is central to the pathogenesis of *JAK2*V617F-negative MPN, genomic studies have identified several mutations in genes coding for proteins involved in this signaling pathway such as Myeloproliferative leukemia (*MPL*), *LNK*, and Casitas B-lineage lymphoma (*CBL*), and more recently and unexpectedly in coding calreticulin (*CALR*). These mutations result in an abnormal overactivation of the JAK/STAT signaling and a selective advantage to the myeloid lineage. However, genomic studies have also shown that MPN are much more heterogeneous disorders than initially thought and that genetic alterations in signaling molecules do not completely resume their entire pathogenesis. This is particularly true for PMF, which, in some aspects is closer to myelodysplastic syndromes (MDS) than to MPN.

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Myeloproliferative Neoplasms are Signaling Disorders Leading to JAK2 Activation

The JAK2 Mutations and MPN

High Prevalence of JAK2V617F in MPN. The *JAK2*V617F mutation is located in the pseudokinase autoinhibitory domain of the

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protein,[2-5] leading to the loss of normal negative regulatory interaction with the kinase domain and thus constitutive activation of the kinase. In the presence of homodimeric type 1 cytokine receptors, JAK2V617F autophosphorylates and mediates the activation of downstream signaling pathways such as the STATs (STAT5, STAT3, and STAT1), the ERK/mitogen-activated protein kinase (MAPK), and the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR).

The different *jak2*V617F murine models mimic the human disorders,[6-9] thus, *JAK2*V617F is the main driver mutation responsible for the myeloproliferative phenotype. However, *JAK2*V617F might not be the initiating molecular event. Indeed, *JAK2*V617F is found associated with other mutations, which by themselves do not give rise to myeloproliferative disorders.

*JAK2*V617F is present in 95% of PV, 65% of ET, and 60% to 50% of PMF. A major question is how a single mutation can give rise to different phenotypes. Strong evidence suggests that in humans, ET is related to the expansion of a heterozygous *JAK2*V617F clone whereas in most PV a homozygous *JAK2*V617F clone is prevalent and results from uniparental disomy at the *JAK2* locus.[10] It has been shown that a JAK2V617F protein threshold level has to be reached to allow maximum constitutive activation of downstream signaling proteins and thus a complete cytokine independency. In murine models, low levels of Jak2V617F give an ET-like phenotype, whereas high levels are associated with a PV-like phenotype.[8,9] Nevertheless, other cellular components play a role in determining the MPN phenotype such as the isoform of STAT being activated by JAK2V617F. STAT5 activation is a key factor in the development of a PV, whereas STAT1 activation in the erythroid lineage has been linked to an ET phenotype due an inhibition of erythroid differentiation.[11,12] Thus, it is possible that germ line determinants including sex might also play an important role in the phenotype of *JAK2*V617F MPN.

In most PV and ET, the *JAK2*V617F clone(s) is associated with wild type *JAK2* clones (presumably normal cells). The mechanism for clonal dominancy of the mutated clone might rely on additional somatic mutations that might either precede or follow environmental changes (inflammation) due to JAK2V617F. None of the murine *Jak2*V617F models gives rise to a PMF. This finding correlates well with the human disease in which several other mutations in genes also found in MDS, are present in addition to *JAK2*V617F and can profoundly alter the hematopoietic differentiation.

Other JAK2 Mutations Might Be Present in MPN. To identify the molecular abnormalities present in the remaining 5% *JAK2*V617F-negative PV, Scott et al sequenced the entire *JAK2* gene in the erythroid cells of these patients and found different mutations in exon 12 (2%-4% of PV), which were not present in ET and PMF.[13] More specifically, these mutations led to the induction of an erythrocytosis phenotype although disease in patients with *JAK2* exon 12–mutation can transform into myelofibrosis. The erythroid colonies from patients who present with *JAK2* exon 12 mutations are rarely homozygous for the JAK2 mutation in contrast to *JAK2*V617F-positive PV. It has been suggested that this relatively pure erythroid phenotype is related to the greater constitutive activity of JAK2 exon 12 compared with JAK2V617F.

Other rare *JAK2* mutations have also been found in MPN.

MPL *Mutations*

MPL is the thrombopoietin (TPO) receptor that belongs to the homodimeric type I cytokine receptor family and requires JAK2 to mediate signaling. Murine models have shown that TPO overexpression leads to a thrombocytosis followed by the development of a myelofibrosis, suggesting that the TPO receptor MPL/JAK2 pathway plays a central role in the development of ET and PMF.[14] Pikman et al sequenced *MPL* and found mutations at codon 515 in exon 10.[15] MPL contains a 5-amino acid amphipathic motif located at the junction of the transmembrane and cytoplasmic domains, which prevents constitutive MPL activation.[16] Substitution of W515 leads to the receptor activation. Five main *MPL* mutations have been reported, all present in exon 10 and affecting 2 amino acids: W515L, W515K, W515A, W515R, and S505N. The most prevalent mutations are W515L and W515K. They are present in 3% of ET and 5% to 10% of PMF, but not in PV.[17] The S505N mutation was initially identified in hereditary thrombocytosis and was also reported in rare sporadic cases.[18] In retroviral murine models, MPL W515L induces a disorder recapitulating human myelofibrosis.[15] A small number of patients with *JAK2* and *MPL* mutations have been reported, probably in different clones.[17]

Other rare mutations in *MPL* also can be present in MPN.

SH2B3 Mutations

SH2B adaptor protein (SH2B3) (LNK), a negative regulator of JAK/STAT signaling, is mutated with a low frequency in patients with MPN with a low frequency (3%).[19] SH2B3 is an adaptor protein that negatively regulates JAK2 activity by binding directly via its Src Homology 2 (SH2) domain. It has also been reported to negatively regulate MPL and erythropoietin receptor (EPOR) signaling.[20] Most of the *SH2B3* mutations are located in the SH2 and plextrin homology domains, and can be found with *JAK2*V617F in the same patient.[21] *Sh2b3*$^{-/-}$ mice present splenomegaly and extramedullary hematopoiesis, and a 3- to 5-fold increase in platelets.[22] In human, *SH2B3* mutations have been reported in ET, PMF, and some pure erythrocytosis and are essentially hypomorphic mutations.

CBL *Mutations*

Casitas B-lineage lymphoma (c-CBL) is an E3 ubiquitin ligase. *CBL* mutations are extremely rare in MPN and are mainly associated with myelofibrosis with a poor prognosis.[23,24] They might be secondary mutations occurring during disease progression to leukemia. *C-CBL* mutations are mainly missense, in the linker-RING finger domain region that is essential to the E3 ubiquitin ligase activity. Mutations are homozygous or heterozygous.

Coding Calreticulin Mutations

Recently, exome sequencing was performed in MPN patients negative for *JAK2*V617F and *MPL* mutations. Recurrent genetic abnormalities were found in exon 9 of the *CALR* gene.[25,26] They are present in 60% to 84% of MPN samples with nonmutated *JAK2* and *MPL*: approximately 70% of ET and 56% to 88% of PMF but not usually in PV. It is also found in refractory anemia with ringed sideroblast with thombocytosis (RARS-T) and very rarely in other myelodysplasia. A 52-base pair (bp) deletion (53%) and a 5-bp

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