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Review

# New pieces of a puzzle: The current biological picture of MPN

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ABSTRACT

Over the last years, we have witnessed significant improvement in our ability to elucidate the genetic events, which contribute to the pathogenesis of acute and chronic leukemias, and also in patients with myeloproliferative neoplasms (MPN). However, despite significant insight into the role of specific mutations, including the *JAK2V617F* mutation, in MPN pathogenesis, the precise mechanisms by which specific disease alleles contribute to leukemic transformation in MPN remain elusive. Here we review recent studies aimed at understanding the role of downstream signaling pathways in MPN initiation and phenotype, and discuss how these studies have begun to lead to novel insights with biologic, clinical, and therapeutic relevance.



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## 1. Introduction

Myeloproliferative neoplasms (MPN) are a phenotypically heterogeneous group of stem-cell derived clonal hematopoietic disorders characterized by abnormal proliferation of terminally differentiated myeloid cells [1]. They are discernible from other myeloid malignancies by the absence of prominent morphologic dysplasia (dyserythropoiesis, dysgranulopoiesis and monocytosis) and retained myeloid differentiation [2]. Eight different MPN entities are distinguished based on the translocation status of the Philadelphia chromosome, the involved myeloid lineages, and the transformation rate to acute myeloid leukemia (AML) [3]. Chronic myeloid leukemia (CML) and the three non-leukemic forms polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) comprise the majority of MPNs and are commonly referred to as the classical forms.

Although PV, ET and PMF share various biological features they represent clinically distinct diseases with heterogeneity in their phenotype

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and natural progression. PV is defined by erythroid predominant, multilineage hyperplasia in the bone marrow. The abnormal red blood cell (RBC) production leads to an increased blood volume and viscosity, which in turn can lead to hemorrhage and thrombosis. Other presenting signs of PV include an increased hemoglobin value accompanied by increased white cell and/or platelet numbers, low erythropoietin (EPO) levels and an enlarged spleen. The hallmark of ET is an elevated number of circulating platelets due to neoplastic megakaryocyte proliferation in the bone marrow. Both PV and ET are indolent disorders with a relatively preserved life expectancy and in most cases the symptomatology can be reasonably controlled by current standard of care treatments [4,5]. On the contrary, the natural course of PMF is more severe and survival of PMF patients is significantly worse [4,6]. PMF patients commonly present with bone marrow fibrosis, progressive anemia, systemic inflammation and extramedullary hematopoiesis, with the latter being associated with splenomegaly and hepatomegaly [7]. At present treatment approaches for PMF patients are not curative, but focus primarily on a reduction of splenomegaly, improvement of hematopoietic function and alleviation of the systemic symptom burden [6,8].

Today it is widely accepted that although there are differences in the clinical presentation of the classical forms of MPNs, the presence of activating mutations in signaling proteins is a feature shared by all MPN subtypes [3]. The discovery of a single point mutation in non-receptor tyrosine kinase JAK2 in almost all PV patients and in 50% of ET and PMF patients was a crucial breakthrough in unraveling the molecular pathogenesis of these non-leukemic forms [9–12]. Since then significant insight has been gained into the molecular mechanisms that drive these clinically distinct disorders, but it has also become clear that additional factors other than clonal proliferation contribute to disease pathogenesis.

In this review, we will first shortly discuss recent advances in the understanding of the (epi-)genetic basis of MPNs. Next, we will center on aberrant signaling mechanisms/pathways and their contribution to the pathogenesis of MPNs Fig. 1. We will also cover the relevance of the bone marrow niche and the role of the host environment on disease development and progression. Lastly, we will survey advances in the development of molecularly targeted therapies and highlight newly emerging treatment strategies.

## 2. Genetic basis of BCR-ABL-negative MPNs

The majority of MPNs arise owing to the presence of chromosomal rearrangements and/or gene mutations that lead to constitutive activation of tyrosine kinase signaling cascades, thus providing the malignant cell with a range of functional advantages [13]. The fusion tyrosine kinase BCR-ABL, which arises from the Philadelphia translocation between chromosomes 9 and 22, was the first activating allele identified and characterized in a MPN [14,15]. CML represents the prototypic MPN and absence of the *BCR-ABL* fusion gene is an important criterion for the differential diagnosis of other MPNs [4]. Until recently the genetic basis of the most common BCR-ABL-negative MPNs remained enigmatic [3,16].

In 2005, four independent research groups found an identical gain-of-function mutation in the important cytokine receptor signaling molecule JAK2 in MPN patients [9–12]. The recurrent somatic G>T point mutation, which causes a valine-to-phenylalanine substitution, V617F, in the pseudokinase domain of JAK2, increases the enzymatic activity of the cytoplasmic tyrosine kinase leading to constitutive activation. This discovery was succeeded by the finding that several additional genes that regulate JAK2 signaling are genetically altered in JAK2V617F-negative cases including gain-of-function mutations in the thrombopoietin receptor (*MPL*) (ET (4%), PMF (11%)) [17,18] and loss-of-function mutations in the *SH2B3* gene (ET (<5%), PMF (<5%), JAK2V617F-negative PV (25%), post MPN AML (13%)) [18], which encodes the negative JAK regulator LNK [19]. In addition, a spectrum of somatic activating mutations within the 12th exon of the *JAK2* gene has been identified ([20] and reviewed in [18]). Following this, murine studies demonstrating that ectopic expression of MPN disease alleles is sufficient to cause a myeloproliferative disease further underscored the importance of aberrant JAK2 function in these diseases (reviewed in [21]). Today, it is widely accepted that deregulated JAK2 signaling is a predominant feature of PV, ET and PMF.

Genetic studies have revealed that the aforementioned activating mutations are mutually exclusive consistent with a redundant role in MPN pathogenesis. More recently a series of studies have discovered somatic disease alleles in concert with JAK-pathway mutations in MPN patients [16]. Several of those genes (*IDH1*, *IDH2*, *DNTM3A*, *ASXL1*, *EZH2*, and *TET2*) encode epigenetic modifiers which regulate histone modification and/or DNA methylation (reviewed in [22]). Moreover, a subset of these oncogenic alleles occur most commonly in blast phase MPN, including *IDH1*, *IDH2*, and *DNMT3A*, and are therefore speculated to drive clonal evolution and progression to AML [23,24]. The Polycomb group proteins ASXL1 [25], EZH2 [26–28], and SUZ12 [29] are the most recent additions to the list of deregulated epigenetic regulators in MPN [30]. Interestingly, next to additional hits in epigenetic genes, it has also been shown that *JAK2* mutations can lead to direct or indirect alterations in chromatin state in hematopoietic cells [31,32].

Importantly, while *JAK2*, *MPL*, and *LNK* mutations are relatively specific for MPN, mutations in epigenetic modifiers are present in a spectrum of myeloid malignancies including AML, myeloproliferative dysplasia (MDS), and juvenile myelomonocytic leukemia (JMML). This fact raises the question whether and to what extent their aberrant function contributes to the specific phenotype of these malignancies, or whether they contribute to disease initiation and/or progression without impacting the clinical phenotype. Continuous advances in genomic technologies promote a rapid expansion of the list of molecular lesions in MPN. However, the relevance and functional consequences of mutations in newly discovered myeloid disease alleles have not been clearly delineated (reviewed in detail in [18]).

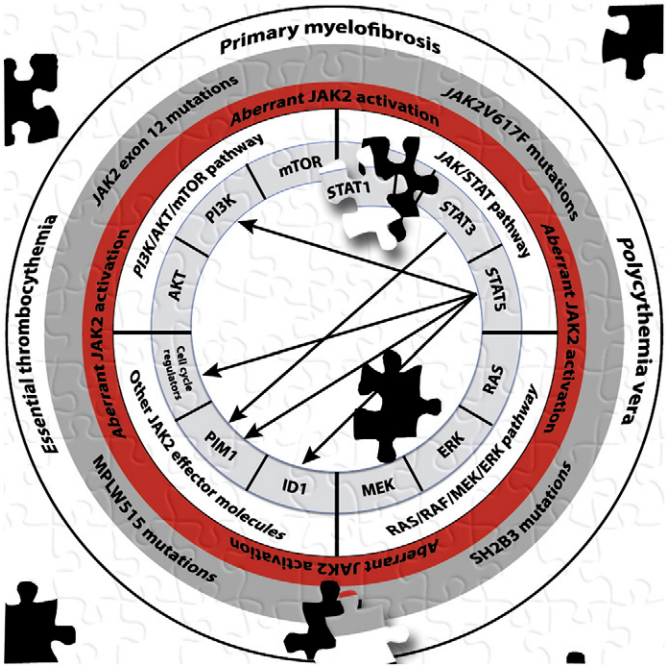


**Fig. 1.** Signaling in MPN patients. Shows the different MPN, and how aberrant JAK2 activation leads to activation of a spectrum of downstream pathways, including STAT3, STAT5, STAT1, MAPK, and PI3K signaling. The relative importance of each of these pathways to MPN pathogenesis and phenotypic pleiotropy has not been delineated.