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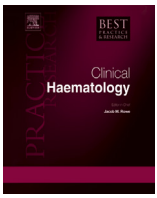

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A primer on genomic and epigenomic alterations in the myeloproliferative neoplasms

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The discovery of the *JAK2* mutation in Philadelphia-chromosome negative myeloproliferative neoplasm (MPNs) in 2005 has heralded an era of rapid genetic discovery in the MPNs. This has lead to substantive gains in the understanding of the pathobiology of these diseases. Importantly, this has also lead to new treatment in the form of JAK inhibitors, as well as to clinical trials targeting other components thought to contribute to disease biology. However, given the number of new genomic alterations uncovered in the last several years, the relative contributions of each mutation to the development of a disease phenotype remains an area of robust investigation. Furthermore, the number of known mutations presents challenges to the practicing clinician in terms of what mutations to test for and the clinical significance of such mutations.

Introduction

The myeloproliferative neoplasms are clonal hematopoietic disorders which were initially described by William Dameshek in 1951 [1]. He initially described essential thrombocythemia (ET), polycythemia vera (PV), primary myelofibrosis (PMF) and chronic myeloid leukemia (CML). An understanding of the genetic basis of myeloproliferative neoplasm began to arise with the description of the Philadelphia Chromosome and subsequent work [2]. However, the genetic basis of the Philadelphia-chromosome

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negative MPNs remained largely unknown until some 54 years after Dameshek's description, with the initial description of the *JAK2*V617F mutation. Since that time, the discovery of novel recurrent genomic alterations in the MPNs has accelerated significantly and resulted in novel biologic insights into these diseases. Most significantly, perhaps, these genetic insights have led to the development of targeted therapeutics (and subsequent FDA approval in the case of Ruxolitinib).

The advent of molecular diagnostics is not without its challenges. Only now are sequencing technologies becoming available for clinical use both in commercial and academic settings. Questions remain about which patients should undergo molecular testing, and for what genetic alterations. More importantly, many questions remain about how to apply genetic information to daily clinical care. Here, we seek to review the major genetic and epigenetic findings of the last several years in MPNs, as well as the biological and clinical implications of these findings. Finally, we discuss possible strategies to marshal such data for use in clinical practice.

Driver mutations in MPN

JAK2

One of the major advances in the field of MPN biology and genetics was the discovery of the *JAK2V617F* mutation by several groups in 2005 (2–6). JAK2 is a non-receptor tyrosine kinase, which is part of a family of tyrosine kinases that includes JAK1, JAK3, and TYK2. The JAK family of kinases are phosphorylated upon ligand binding to cytokine receptors (most notably granulocyte colony-stimulating factor, thrombopoietin, and erythropoietin) [3,4] and serve to further phosphorylate downstream targets, thus serving an important role in hematopoietic cell function. The *JAK2V617F* mutation results in constitutive activation of the kinase with resulting downstream signaling. As well, JAK2 can act as an epigenetic modifier by phosphorylating histone H3 or the arginine methyltransferase PRMT5 [5–7], and JAK2 mutants have been demonstrated to bind to PRMT5 with greater affinity than wildtype JAK2 (resulting in impairment of PRMT5 function). Notably, downregulation of PRMT5 has been demonstrated to result in erythroid differentiation, suggesting that the *JAK2*V617F mutation may contribute to an MPN phenotype by more than one mechanism [8].

Biological validation of the effects of the *JAK2*V617F mutation has been performed by several groups in murine models. Expression of *JAK2*V617F in a murine transplant model results in erythrocytosis in transplanted mice, but not thrombocytosis (depending on genetic background). Myelofibrosis has also been reported in these models as well [9–12].

The *JAK2*V617F mutation is not specific to one MPN, and has been reported in 90–95% of patients with PV, and 50–60% of patients with ET and PMF [13–17]. As well, *JAK2* mutations have been noted in other myeloid malignancies such as MDS, with predominance in the refractory anemia with ringed sideroblasts and thrombocytosis (RARS-T) subtype [18].

Apart from the *JAK2*V617F, mutations in exon 12 of *JAK2* has been identified which are gain-of-function mutations [19,20]. Expression of these mutations in cell lines leads to factor-independent growth and recapitulates phenotypes observed in murine *JAK2*V617F transplant models.

MPL

An activating mutation in the thrombopoietin receptor *MPL* (*MPL*W515L) was described in MF patients who were negative for the *JAK2*V617F mutation [21]. This mutation was found to impart cytokine-independent growth on cell lines, and produces a phenotype similar to MF in murine bone marrow transplant models (organomegaly, thrombocytosis, leukocytosis, reticulin fibrosis). *MPL* mutations have also been noted in patients with ET (*MPL*W515 L/K) [22] as well as familial ET [23], but not in patients with PV.

CALR

JAK2 and *MPL* mutations collectively account for approximately half of MF and ET cases. However, until recently it the genomic alterations accounting for the remainder of cases was unknown. In 2013,