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Relationship between disease biology and clinical phenotype in myeloproliferative neoplasms

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Take home messages

- Canonical mutations in JAK2, CALR, and MPL, mutations in other cancer genes, germline genetic backdrop, and patient characteristics interact to determine myeloproliferative neoplasm phenotype.
- Disease transformation is often associated with the acquisition of further somatic mutations across an array of cancer driving genes.

Introduction

Over the last 15 years, significant advances have been made in our understanding of the molecular basis of myeloproliferative neoplasms (MPNs). The discovery of mutations in *JAK2*, *MPL*, and subsequently *CALR*, has led to an identifiable molecular driver of disease in over 85% of patients. Mutant JAK2 and MPL are known to result in excessive intracellular JAK-STAT signaling, and in recent years, an active area of research has been to understand precisely how mutant CALR also instigates myeloproliferation. Disease classification in MPNs remains an ongoing debate due to the recognition of heterogeneity and overlapping features across traditional MPN entities and our increasing understanding of the genomic landscape of these disorders. We are also uncovering the biological basis of disease evolution and beginning to understand how additional mutations may drive the phenotype of myelofibrosis (MF) and leukemic transformation. However, the factors that determine mutation acquisition and clonal expansion in the first place still remain incompletely understood, particularly, as many of the somatic mutations found in MPNs are also noted in the blood of healthy ageing individuals that do not suffer from hematological disease. In the future, a more complete understanding of MPNs from its early origin to late outcomes will aid our endeavors to predict, treat, and prevent disease progression in patients.

Current state of the art

We have a better appreciation of the factors that underlie phenotypic heterogeneity across MPNs.[1] JAK acts downstream of several cell surface cytokine receptors, including those for erythropoietin, thrombopoietin, and GM-CSF, and thus, activating mutations in *JAK2* are variably associated with increased erythropoiesis, increased thrombopoiesis, and a mild leukocytosis.[2] $JAK2^{V617F}$ is found in over 96% of patients with polycythemia vera (PV), and just over half of patients with essential thrombocythemia (ET) or MF. In the presence of mutant JAK2, several factors have been shown to influence whether a patient presents with a phenotype more in keeping with PV or ET,[3] for example, a higher mutant allele burden is more frequently associated with PV, homozygosity for $JAK2^{V617F}$ has been shown to be associated with PV as well as drive erythrocytosis in a murine model of MPN, mutations in exon 12 of *JAK2* are specifically associated with erythrocytosis and a PV phenotype probably through excessive signaling via the Erythropoietin receptor,[4] and the acquisition of $JAK2^{V617F}$ prior to the acquisition of mutations in other genes is more frequently observed in PV, whereas later acquisition of $JAK2^{V617F}$, subsequent to mutations in other genes, is more frequent in ET. In addition to differences in the type or burden of somatic mutations, several germline genetic factors predispose to MPN,[5,6] and germline polymorphisms that contribute to the normal variation in blood count parameters may also influence whether a patient is given a label of PV or ET at diagnosis.[*7] Finally, patient demographics

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such as increasing age and male sex are also associated with PV. Mutations in *MPL* specifically result in excessive signaling downstream of the receptor for thrombopoietin, resulting in chronic phase MPNs characterized by isolated thrombocytoses and increased myelofibrotic transformation.[2,*7,8] Indeed, mutant CALR has been shown to physically interact with MPL in a manner requiring both the mutant C-terminus and the lectin binding domain, leading to constitutive activation of downstream signaling and an MPN phenotype that recapitulates many of the features of *MPL*-mutated disease.[9,10,11,*12] How and where this interaction takes place, and whether components of the mutant protein can be targeted therapeutically remain active areas of research.

In addition to mutations in the canonical driver genes, roughly half of patients with ET/PV and the majority of patients with MF, harbor additional somatic mutations in other cancer genes.[*7,13,14] The function of these genes is diverse, and include regulation of DNA methylation (eg, *DNMT3A*, *TET2*), chromatin modification (eg, *ASXL1*, *IDH1/2*), intracellular signaling (eg, *NRAS*, *GNAS*), mRNA splicing (eg, *SRSF2*, *U2AF1*, *SF3B1*), and DNA repair (eg, *TP53*). Mutations in these genes are more prevalent in MF, and when present in chronic phase, are associated with increased risk of MF transformation.[*7,15] We are beginning to understand how some of these mutations promote disease progression, through affecting hematopoietic stem cell self-renewal, differentiation, and DNA repair.[16,17,18,*19,20] Mutations in *TP53* and/or deletion of chromosome 17p have been shown to be associated with subsequent blast transformation (Fig. 1).[13] The significance of very low burden mutations in some of these genes remains unclear.[21] It is worth bearing in mind that disease evolution may not entirely be genomically encoded. Several prognostic scores,[22,23] including more recent personalized prognostic modeling,[*7] have shown the value of other variables such as the presence of splenomegaly, blood counts, and transfusion status, and patient demographics, as independent predictors of disease evolution, suggesting that these parameters capture elements of MPN disease biology that are not represented by the current tumor genomic landscape. Integrating genomic information from an MPN, together with clinical parameters and patient demographics, has been shown to accurately predict disease and patient outcomes.

Bone marrow is a highly replicative tissue, and in recent years, the number of hematopoietic stem cells, their rate of division, and the rate of somatic mutation acquisition over time has been estimated.[*24,25] The phenomenon of age-related clonal hematopoiesis has highlighted that somatic driver mutations can be identified in the blood in the absence of clinical disease.[26,*27] It is likely that in addition to mutation acquisition, additional factors, such as aging, the bone marrow microenvironment and therapy impact on whether a cell that harbors a driver mutation subsequently clonally expands.

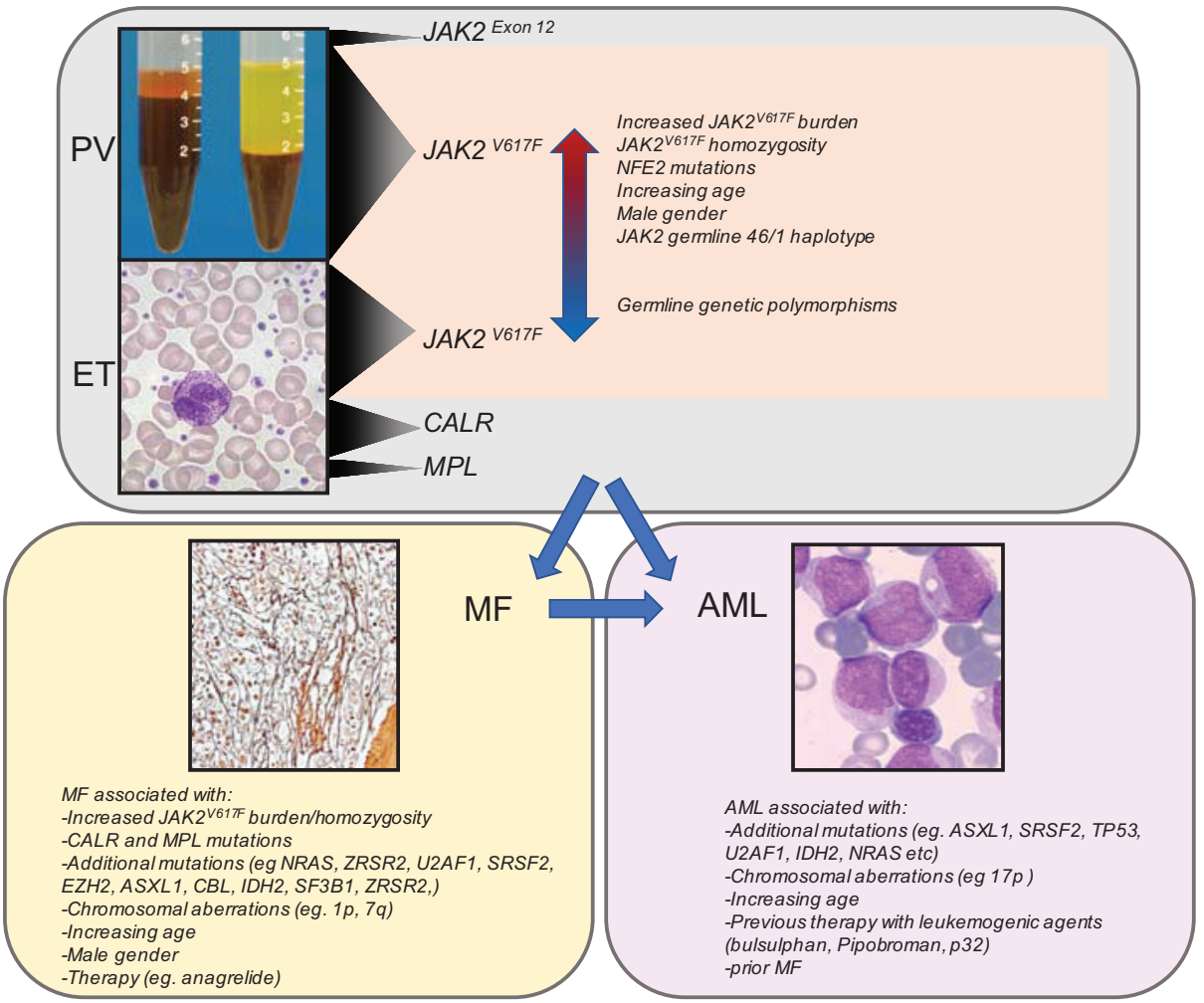

Figure 1. Figure illustrates the MPN subtypes, disease evolution, and some of the factors that are known to contribute to the different phenotypes.

Future perspectives

How driver mutations are acquired in the genome, and what effect they have on clonal dynamics within the bone marrow under different ages and bone marrow environments remain important questions for the future, that will aid our understanding of how these diseases originate. An ongoing challenge is that our current therapies do not act specifically on the mutant clone, nor do they demonstrate significant disease modifying ability. The mechanism by which combinations of mutations drive disease evolution is an active area of research through which novel strategies for targeting disease progression may be unearthed. With ongoing efforts to improve our understanding of the factors that contribute to MPN phenotype, heterogeneity, and disease evolution, we are now better equipped to identify groups of patients with shared disease biology. Combining this information with treatment response data will help to target both existing and novel therapeutic agents to the right patients.

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