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COMMENTARY

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Molecular pathogenesis of myeloproliferative neoplasms: Where do we stand in 2023?

Violaine Havelange[1,2] | Stefan N. Constantinescu[1,2,3,4,5]

[1]Université catholique de Louvain and de Duve Institute, Brussels, Belgium

[2]Cliniques universitaires Saint-Luc, Brussels, Belgium

[3]Ludwig Institute for Cancer Research Brussels, Brussels, Belgium

[4]WelBio Department, Wel Research Institute, Wavre, Belgium

[5]Ludwig Institute for Cancer Research, Nuffield Department of Medicine, Oxford University, Oxford, UK

Correspondence
Stefan N. Constantinescu, Université catholique de Louvain and de Duve Institute, Brussels, Belgium.
Email: stefan.constantinescu@bru.licr.org

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Next-generation sequencing (NGS) in clinical practice and whole exome sequencing (WES) in research have in the last years accelerated the understanding of the molecular pathogenesis of myeloproliferative neoplasms (MPNs).[1] The classical *BCR-ABL1*-negative MPNs arise from clonal proliferation of a single hematopoietic stem cell that will be responsible for the excessive production of mature myeloid cells.[2] This heterogeneous group of disease includes three subtypes: polycythemia vera (PV) involving predominantly the erythroid lineage, essential thrombocytemia (ET) with overproduction of megakaryocytes and platelets and primary myelofibrosis (PMF) characterized by fibrosis and splenomegaly. The acquisition of one gain-of-function "disease phenotypic driver" mutation (*JAK2*V617F, *CALR*, *MPL*) in a single hematopoietic stem cell can initiate and promote MPN disease without requiring additional cooperating mutation. As reported in this issue of the *American Journal of Hematology*, single-cell DNA sequencing studies reveal that MPNs appear to be oligoclonal rather than monoclonal (Figure 1).[3] The three "disease phenotypic driver" mutations will lead to constitutive activation of the JAK/STAT signaling pathway, which is also found in triple-negative MPN patients. The time between the acquisition of the "disease phenotypic driver" mutation and the disease phenotype may be prolonged over decades.[2] MPN "disease phenotypic driver" mutations (mainly *JAK2*V617F) can be detected in certain individuals with normal blood counts that exhibit clonal hematopoiesis of undetermined potential.[4,5] Mathematical models of prediction indicated that *CALR* mutations may be acquired later in life even if *CALR*-mutated MPNs develop on average a decade before *JAK2*V617F MPNs.[6] However, *JAK2*V617F and *CALR* mutations were both detected in utero in some patients with a long latency before the development of the disease.[7,8]

The *JAK2*V617F mutation is the most frequent disease phenotypic driver mutation detected in >95% of the PV and in 50%–60% of ET and PMF. JAK2 is a nonreceptor tyrosine kinase, which is associated with the cytoplasmic domain of several cytokine receptors including MPL, EPOR, and G-CSF-R. *JAK2*V617 is a somatic G to T mutation at nucleotide 1849 in exon 14 of *JAK2* resulting in the substitution of valine to phenylalanine at codon 617. This gain-of-function mutation is in the pseudokinase domain and will activate the kinase domain promoting dimerization of the mutated pseudokinase domain via a network of aromatic interactions, thus allowing dimerization and activation of the kinase domain and removing the negative regulation of the kinase domain.[9–13] *JAK2*V617F will constitutively activate the three main myeloid homodimeric receptors (EPOR, G-CSFR, TPOR/MPL) and induce three phenotypes by activating mainly three signaling pathways STAT, PI3K/AKT/mTOR, and RAS/MPK. *JAK2*V617F can be heterozygous or become homozygous after mitotic recombination. Homozygous mutation is more frequent in PV patients. The variant allele frequency (VAF) in granulocytes is usually low in ET and higher in PV (> 50%) and close to 100% in post-PV or post-ET MF.

The mutation of the calreticulin (*CALR*) is detected in 25%–30% of ET and in 20%–25% of PMF patients. Calreticulin is a chaperone protein that is involved in the quality control of the glycoproteins and in calcium metabolism. The most prevalent *CALR* mutations are mainly deletion of 52 bp (del52 – type 1) and insertion of 5 bp (ins5- type 2)

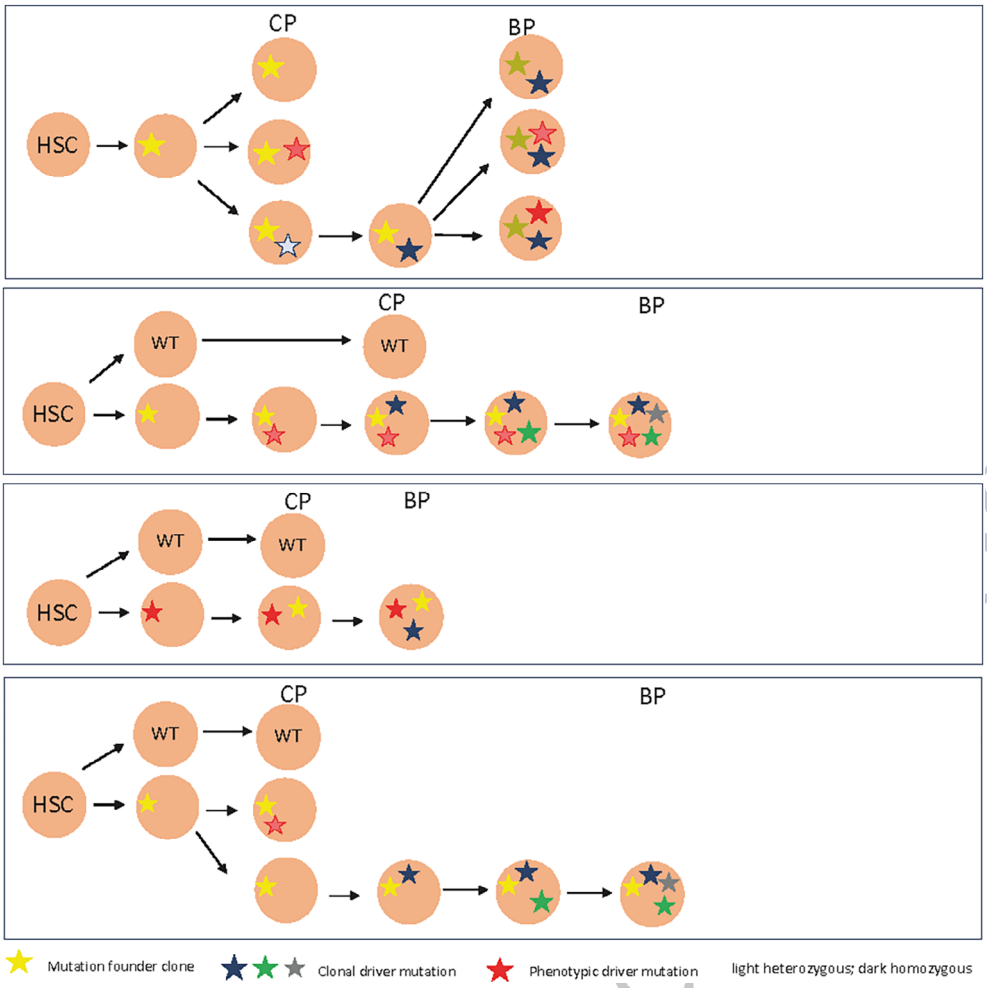

FIGURE 1 Calabresi et al.[3] identified four patterns of clonal evolution from the HSC to the chronic phase (CP) MPN and blast phase (BP) by analyzing 10 patients by single-cell sequencing at diagnosis of CP and upon evolution to BP.

in the exon 9, but more than 55 other mutations have been described that accomplish the same +1 frameshift. These frameshift mutations will result in a new C-terminus domain with positively charged hydrophobic residues lacking the KDEL endoplasmic reticulum (ER) retention signal.[14] The differences between del52-like and ins5-like mutations, denoted as type 1 and type 2, also result from maintaining certain negatively charged residues from wild-type CALR in ins5/type 2 mutants, while del52/type 1 mutants eliminate all remaining negatively charged residues. The CALR mutant C-terminus domain forms a dimer and will bind to negatively charged patches on TPOR extracellular domain while the N-terminus lectin domain of CALR will bind to the N-glycans on TPOR extracellular domain Asn117; this bi-partite interaction induces TPOR dimerization, leading to a persistent JAK2 activation.[14–18] The CALRm/TPOR complex will move to the cell surface or be secreted as a rogue cytokine, which will subsequently bind to mutated cells.[17] CALR mutant will also impair calcium retention in the ER and activation of an ER stress response. The VAF of *CALR* mutation in the granulocytes in ET is usually high (40%).

The myeloproliferative leukemia protein also known as thrombopoietin receptor (*MPL/TPOR*) mutations are rare and detected in 5% of PMF and 10% of ET patients. The main TPOR functions are the regulation of the platelet production and the maintenance of hematopoietic stem cells. *MPL* mutations are prevalent in the cytosolic juxta-membrane domain at W515 (W515L/W515K). These gain-of-function mutations result in a ligand-independent TPOR dimerization of the transmembrane domain, a constitutive activation of TPOR, an activation of JAK2 signaling pathways, and TPO-independent megakaryocytopoiesis.[19–22] Mutations in *MPL* also have been described in the transmembrane domain (S505N).[23] The transmembrane and juxtamembrane mutations induce dimerization of the TPOR transmembrane domain and unraveling (flexibility) of the region downstream the transmembrane domain, allowing JAK2 kinases to cross-phosphorylate and activate each other.[24,25]

A fascinating aspect is that while both CALR and MPL/TPOR mutants function by persistent TPO-independent activation of TPOR itself, the phenotype, age, and evolution of the diseases are not identical, the *MPL/TPOR* mutated patients being closer to *JAK2*V617F patients than to *CALR*-mutated patients. It remains to be seen whether CALR mutant proteins activate TPOR in a different way or with different kinetics than mutations in TPOR itself, or whether other functions of mutant CALRs related to ER stress, NFkB, and Ca2+ would explain these differences.[26]

The "disease phenotypic driver" mutation influences the clinical phenotype, prognosis, and outcome. Young male patients with *CALR*-mutated ET present lower hemoglobin and white blood cell counts, but higher platelet counts compared with patients with *JAK2* and *MPL*

mutations in MPNs.[27–29] *CALR*-mutated PMF patients have a lower WBC count and a higher platelet count than *JAK2*-mutated patients.[30,31] *CALR*-mutated PMF patients have a lower risk of developing anemia requiring transfusion, thrombocytopenia, and marked leukocytosis compared with the *JAK2*V617F PMF patients.[30,31] *CALR*-mutated ET and PMF patients have a lower risk of thrombosis (divided by two) than *JAK2*-mutated patients.[27,31,32] *CALR*-type 1 (del52-like) mutated patients seem to exhibit an increased risk of fibrotic transformation compared with *JAK2*-mutated patients.[33] *CALR*-mutated PMF have an indolent clinical course and a better survival rate compared with *JAK2* or *MPL* or TN PMF patients.[30,31,34]

The NGS data revealed additional somatic mutations called "clonal driver" mutations in some but not all MPN patients. These mutations may be associated with the phenotype and have a prognostic role in MPN patients. The most frequent MPN "clonal driver" mutations involved *TET2*, *DNMT3A*, *ASXL1*, *EZH2*, *SRSF2*, and *SF3B1*. These mutations are not MPN-specific. They are found in up to 20% of PV, up to 20% of ET, and up to 40% of PMF patients. Additional mutations usually occur after the "disease phenotypic driver" mutation and may accelerate the *JAK2*V617F-driven clonal expansion and contribute to disease progression and leukemic transformation. They can also occur as early events that facilitate the clonal emergence and the acquisition of the *JAK2*V617F mutation.[35] PV and ET showed the same number of associated mutations, but MF patients present a higher number of mutations that are more heterogeneous.[36] *TET2* mutations are the most common and are detected in 10%–20% of classical MPN. *DNMT3A* mutations are detected in 5%–10% of MPN patients. *TET2* and *DNMT3A* mutations are usually required for *JAK2*V617F-driven disease. *CALR* mutation is associated with fewer additional mutations. The order of the acquisition of the mutation influences the clinical phenotype and the prognosis.[37] *JAK2* first is associated with PV while *TET2* first is associated with ET or MF. *JAK2* first is associated with a higher risk of thrombosis. *DNMT3A* first is associated with ET.

Tefferi et al. showed that spliceosome mutations are associated with a decrease in overall survival (*SF3B1*, *SRSF2* in ET and *SRSF2* in PV) and an increased risk of myelofibrosis evolution (*U2AF1*, *SF3B1* in ET).[38] Forty to sixty percent of MF patients harbor deleterious mutations. High molecular risk (HMR) mutations included *EZH2*, *IDH1/2*, *SRSF2*, *ASXL1*, and *U2AF1*. The presence of any HMR mutation in PMF patients confers a shorter overall survival. The detection and the number of HMR mutations are included in the MIPSS70+ version 2.0 and GIPPS prognostic scores. These prognostic scores are used for the decision of transplant. The myelodepletive–cytopenic phenotype of MF is characterized by a low *JAK2*V617F VAF frequency or a wild-type *JAK2* and somatic mutations involving the spliceosome, epigenetic, and apoptosis pathways.[39] Myeloid mutations including HMR and *U2AF1* mutations are enriched in cytopenic MF patients, suggesting that this phenotype is caused less by JAK/STAT activating mutations and more by the evolution of an aggressive subclone with several clonal driver mutations.[39,40] The myelodepletive phenotype is more frequently observed in PMF patients and is associated with a shortened survival.

Leukemic transformation of MPN holds still a dismal prognosis. The mutational profile of secondary AML (sAML) involved frequently mutated *TP53*, *ASXL1*, *RUNX1*, *EZH2*, *IDH1/2*, *SRSF2*, and *SH2B3*. These mutations are acquired at the time of leukemia transformation or are already detected at a very low allele frequency in chronic phase, where they can be missed by bulk DNA sequencing and are detected by single-cell DNA sequencing approaches such as Tapistry.[3,41] In some patients, *JAK2*V617F or *CALR*-mutated drivers are not detected in the leukemic blasts, suggesting that a secondary AML clone arises from a common mutated HSC before the acquisition of a disease driver like *JAK2*V617F or from another HSC.[42] The molecular landscape of post-PV/ET AML is different from post-PMF. *TP53* is the most frequent mutated gene in sAML and is mainly involved in post-PV or post-ET AML.[43] Long-term transformation frequently involves *TP53* mutation. *TP53* mutations can be detected at a very low VAF in chronic-phase MPN patients. The leukemic transformation will require the loss of the second *TP53* allele or another genetic event.[44] Short-term transformation involves more complex additional mutations such as *IDH1/2*, *DNMT3A*, *EZH2*, *U2AF1*, and *RUNX1* not detectable in the chronic phase.[43] *ASXL1* is more frequently involved in post-PMF AML.[45]

Single-cell sequencing advanced our understanding of the progression of MPNs to sAML. With respect to *TP53*-mutated sAML a recent study analyzed longitudinal cohorts of MPN and sAML patients by simultaneously single-cell sequencing DNA and RNA, allowing allelic resolution.[46] Using analysis of antecedent *TP53* heterozygous clones, a role for inflammation was established in the progression to sAML.[46] In this journal, Calabresi et al. analyzed a cohort of MPNs that evolved to sAML by the single-cell DNA sequencing Tapestri approach combined with amplicon polyploidy. This analysis showed that MPNs may in fact be oligoclonal and that CNV in certain genes appear to be recurrent events in transformation. While the majority of sAML emerged from the driver disease clone maintaining, for example, *JAK2*V617F or *CALR* mutation, some (3/10) did not (Figure 1). A major question is whether in such cases the clone at the chronic stage triggers paracrine changes in another stem cell that becomes the course of AML. *EZH2* emerged as the gene most frequently affected by single nucleotide and CNV, and this was validated at RNA seq and chromatin accessibility levels in one patient. Single-cell sequencing holds thus the potential to identify clonal complexity early on, when the future sAML clone is a minor clone at the chronic phase (Figure 1).[3,26,41,46,47] Approaches allowing long-sequence determination (NanoPore technology) are being tested in many laboratories and it will be of great interest to compare the results obtained by various single-cell sequencing approaches.

In conclusion, the deeper understanding of the molecular pathogenesis of MPN since 2005 has already allowed us not only to understand the physiopathology of the disease but also to develop diagnostic tools, prognostic scores, and new therapies. In the future, targeted therapies will be added to conventional therapies and adapted to each MPN molecular profile. The knowledge of the biochemistry of the mutations in the MPN cells allows the first development of immunotherapies and will participate in the progress of this promising therapy.

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CONFLICT OF INTEREST STATEMENT

Stefan N. Constantinescu is a co-founder of MyeloPro Diagnostics and Research GmbH, Vienna.

ORCID

Stefan N. Constantinescu https://orcid.org/0000-0002-8599-2699

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