Introduction to a review series on myeloproliferative neoplasms

According to PubMed, the adjective “myeloproliferative” was used for the first time in the title of a scientific paper by William Dameshek in 1951, when he published an editorial in Blood entitled, “Some speculations on the myeloproliferative syndromes.” In this article, featured in the recent Blood Flashback series, Dameshek introduced the concept of myeloproliferative disorders as conditions characterized by excessive proliferation of hematopoietic precursors in the bone marrow and excessive production of mature blood cells. He included in this category chronic granulocytic leukemia, polycythemia vera (PV), idiopathic or agnogenic myeloid metaplasia of spleen, megakaryocytic leukemia, and erythroleukemia. Although some of these names are no longer in use, Dameshek’s editorial represents a remarkable example of visionary leadership.

In 2008, to underscore the clonal nature of myeloproliferative disorders, the authors of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues introduced the name “myeloproliferative neoplasms” (MPNs). The revised version of this classification includes the following MPNs: chronic myeloid leukemia (CML), BCR-ABL1; chronic neutrophilic leukemia (CNL); PV; primary myelofibrosis (PMF); essential thrombocythemia (ET); chronic eosinophilic leukemia, not otherwise specified; and MPN, unclassifiable. In addition, the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues comprises the myeloid/lymphoid neoplasms with eosinophilia and rearrangements of PDGFRα, PDGFRβ, FGFR1, or with PCM1-JAK2.

Over recent years, there have been tremendous advances in our understanding of the genetic basis of MPNs and related myeloid neoplasms. Milestones in this field include the following discoveries: (1) the FIP1L1-PDGFRα fusion gene in patients with hypereosinophilic syndrome in 2003; (2) the unique JAK2 (V617F) mutation in patients with classical MPNs in 2005; (3) oncogenic CSF3R mutations in patients with CNL in 2013; and (4) somatic mutations of CALR in classical MPNs in 2013.

The following series of reviews describes the latest advances in our understanding of the genetic basis of MPNs and related myeloid neoplasms, as well as of its clinical relevance:

- William Vainchenker and Robert Kralovics, “Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms”
- Elisa Rumi and Mario Cazzola, “Diagnosis, risk stratification, and response evaluation in classical myeloproliferative neoplasms”
- Alessandro M. Vannuchi and Claire N. Harrison, “Emerging treatments for classical myeloproliferative neoplasms”
- Andreas Reiter and Jason Gotlib, “Myeloid neoplasms with eosinophilia”
- Julia E. Maxson and Jeffrey W. Tyner, “Genomics of chronic neutrophilic leukemia”

In the first review, Vainchenker and Kralovics examine the genetic landscape of MPNs. They subdivide mutant genes into MPN drivers and non-MPN drivers. Through gain-of-function mutations, MPN-driver genes activate the cytokine receptor/JAK2 pathway and their downstream effectors. On the other hand, through loss-of-function mutations, myeloid tumor-suppressor genes act as dominant negative, or via haploinsufficiency, or via complete homozygous loss, and contribute to phenotypic variability, phenotypic shifts, and progression to more aggressive myeloid neoplasms. In the second review, Rumi and I examine the 2016 revision of the World Health Organization (WHO) classification of classical MPNs, and then discuss the need for a deeper integration of clinical features, morphology, immunophenotype, and genetics for defining and managing MPNs. In the third review, Vannuchi and Harrison describe current therapies for ET, PV, and PMF, focusing on emerging aspects within this diverse field. In the fourth review, Reiter and Gotlib examine the myeloid neoplasms with eosinophilia, focusing on the myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRα, PDGFRβ, or FGFR1, or with PCM1-JAK2. Finally, Maxson and Tyner discuss the genomics of CNL, a distinct MPN with a high prevalence of mutations in the CSF3R gene. They also examine a related disorder, atypical CML, which has higher genetic complexity, including a high prevalence of somatic mutations in the SETBP1 gene.

Collectively, these reviews summarize the last 15 years or so of work in the field of MPNs and related myeloid neoplasms, and provide a perspective for future studies. I hope that Blood readers find this review series of interest.

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References

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