Comment on Tefferi et al, page 2507

Life, genes, and death in Ph− MPNs

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In this issue of Blood, Tefferi et al make the important observations that polycythemia vera (PV) is not a continuum from essential thrombocythemia (ET), that survival in ET is less than matched controls but of longer duration than in patients with PV and primary myelofibrosis (PMF), and that “triple negative” mutational status in PMF is an important adverse risk factor for blast transformation. Genetic profiling should be integrated into classical methods for profiling these diseases.1

Even before William Dameshek described the interrelationship of the myeloproliferative diseases, hematologists noted their frequent termination in a phenotypic picture resembling acute myeloid leukemia.2 The discovery of the Philadelphia chromosome (Ph+) permitted the division of this group of diseases into Ph+ chronic myeloid leukemia (CML) and the main Ph− subgroup encompassing PV, ET, and PMF. The development of new chemotherapeutic agents and their enthusiastic use beginning in the 1950s for all types of leukemia, but especially acute leukemia, required a reliable demarcation of the blast phase of CML. Nearly a half century ago, this was based on the presence of the Ph+ chromosome and the percent blasts in blood or marrow,3 a set of criteria which has survived the test of time, and is applicable to the Philadelphia chromosome negative myeloproliferative neoplasms (Ph− MPNs) as well. Little interest existed in identifying other risk factors because the chemotherapeutic results of blast-phase Ph− MPNs were even less satisfactory than those of patients with CML, especially after the advent of the tyrosine kinase inhibitors.

The discovery of the Janus kinase 2 (JAK2) mutations4 (seen in nearly all patients with PV and in slightly more than half of the patients with ET and PMF) and the myeloproliferative leukemia virus oncogene (MPL) mutation5 (in 5%-10% of patients with ET and PMF) rekindled enormous interest in the Ph− MPN diseases. Clinical and basic science studies led to an improved understanding of these disorders. It was suggested that ET and PV were a continuum of one basic disease.6 Studies of risk factors for treatment of the Ph− MPNs assumed importance, as frenzied activity by pharmaceutical companies followed in order to develop inhibitors of JAK2 mutations. The most recently discovered genetic abnormality, calreticulin (CALR) exon 9 insertions/deletions,7 which presumably upregulates JAK2 activity, has been found in about 25% of patients with ET and in 30% of patients with PMF, respectively, but not in PV. Thus, CALR affords another way to clinically delineate one Ph− MPN from another. In a most timely and important article, Tefferi et al have assessed in perspective the clinical and biological importance of JAK2/MPL/CALR mutational studies. They have combined nearly 1600 patients from the Mayo Clinic (Rochester, MN) and centers in Florence, Italy, and Bergamo, Italy, analyzing their phenotypic and genotypic characteristics especially regarding survival and blast transformation. They offer evidence that ET and PV are not a continuum of one disease, but are separate entities based upon morphologic and clinical analysis. Survival of ET patients is prolonged but not equal to that of a matched normal population, but longer than that of patients with PV and PMF. Of the various permutations of the 3 genes, “triple-negative” PMF patients seem to be a breed apart and bear special watching for the development of blast crisis. The authors wisely advise that their analyses should be interpreted and interdigitated with other observations such as the Dynamic International Prognostic Scoring System plus8 and other identified mutations associated with an adverse prognosis such as the ASXL1 gene.

Some caveats exist. Despite the large number of patients, the results should be considered “preliminary” because the study was retrospective, based upon 2008 World Health Organization (WHO) criteria9 for which some reservations have been expressed, especially in the case of PV.10 Patient selection for mutation analysis rested upon availability of archival DNA. Duration of follow-up differed between the Mayo and Italian patients as did the number of patients followed to death.

Nevertheless, Tefferi et al make the relevant points that the diseases remain distinguished not only by their genetic profile but also by their phenotypic characteristics and clinical course. Moreover, mutations have not supplanted the need for morphologic and otherwise classical methods for disease distinction which have prognostic and therapeutic relevance. Thus, the final word has not been written but this article is important because it emphasizes the need for correlating the new genetic markers with the classical methods, including examination of marrow biopsies, for evaluating these diseases.

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Hematopoiesis & Stem Cells

Comment on Padrón-Barthe et al, page 2523

The hemangioblast revisited

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“What’s in a name, that which we call a hemangioblast
By any other name would follow the same fate.”
—Paraphrased from Shakespeare

In this issue of Blood, Padrón-Barthe et al explore the role of the hemangioblast as the cell of origin for yolk sac blood and endothelium.¹

Although recent years have seen a significant increase in our understanding of the complex onset of hematopoiesis in the embryo,² the precise cellular origin of blood cells remains associated with recurrent controversies: is the adult mammalian hematopoietic system ultimately derived from the dorsal aorta or the yolk sac? Is blood derived from a hemangioblast, hematogenic endothelium, or a combination of both? Clarifying such controversies will be important for informing studies aimed at de novo generation of blood cells for clinical purposes. Through in vivo clonal analysis of early mouse hematopoiesis, Padrón-Barthe and colleagues find little evidence for the hemangioblast as the common cell of origin for both blood and endothelium.¹ Their results provide important in vivo support for previous ex vivo fate mapping studies in the mouse³,⁴ and prompt us to revisit the concept of the hemangioblast.

A common origin of blood and endothelium was first proposed at the beginning of the last century. Building on the work of Sabin, Maximov, and others, it was Murray who in 1932 coined the term “hemangioblast” to indicate the thickenings of the mesoderm in the chick yolk sac, the mesodermal “masses” located at the sites where later the blood islands emerge.⁵ It is worth noting that Murray defines the hemangioblast as a population of cells, which as a whole gives rise to the blood and endothelium of the blood islands. At the time, he could not say whether extrinsic cues determine the fate of individual hemangioblast cells or whether inherently different precursors for the 2 lineages coexist within his hemangioblast. Fast forward to the 1990s when a clonal mesodermal precursor for blood and endothelium was identified in embryonic stem (ES) cell differentiation cultures,⁶ the blast colony-forming cell (BL-CFC). This cell was thought to be the in vitro equivalent of the in vivo hemangioblast, implying a conceptual change, where “hemangioblast” no longer represents a population of cells, but a clonal bipotential progenitor to blood and endothelium. However, in contrast to the original hemangioblast that had its physical presence in the mesodermal masses of the prospective blood islands, the in vivo site of residence of this clonal hemangioblast remained uncertain. It was not until the identification of low numbers of BL-CFC in the primitive streak of the E7.5 mouse embryo⁷ that this newly defined hemangioblast found its place. The BL-CFC was reported to give rise to primitive erythrocytes, as well as other hematopoietic progenitors in culture. More recently, a closer examination of ES cultures placed the BL-CFC and a putative in vitro equivalent of hemogenic endothelium in 1 linear pathway,⁸ lending support for a model of developmental hematopoiesis in which the hemangioblast gives rise to blood cells through a hemogenic endothelial intermediate.⁹ As, so far, no hematopoietic stem cells have been derived from ES cell cultures, this model has been restricted to yolk sac hematopoiesis.

In their current work, Padrón-Barthe and colleagues assess the in vivo relevance of the clonal hemangioblast and the hemogenic endothelium to yolk sac hematopoiesis. They use an inducible Cre mouse model where Cre is expressed from the ubiquitous pOl1 locus. Injection of a low dose of 4-hydroxy-tamoxifen early in gestation results in the random genetic labeling of single cells of (pre)gastrulation stage embryos. These cells grow out to clones, and labeled clones contributing to the yolk sac blood islands are analyzed for the presence of blood and/or endothelial cells. The strength of this genetic labeling approach over previous mouse studies³⁴ is that it is clonal, does not require embryo manipulation, and, importantly, labeling and tracing occur entirely in vivo. Remarkably, the majority of the labeled clones contain either blood or endothelial cells, whereas only a small percentage harbor both lineages. These bilineage clones appear to result from labeling

REFERENCES

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