SPECIAL REPORT

The polycythemia vera stem cell

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Polycythemia vera (PV) is the most common chronic myeloproliferative disorder (MPD), having an incidence of 2.5 per 100 000 MPD cases. PV is a clonal stem cell disease causing the unregulated production of morphologically normal red cells, white cells and platelets. The resulting erythrocytosis distinguishes PV from all other chronic MPDs. There is currently no specific clonal diagnostic marker for PV. In 2005, James *et al.*¹ reported that a specific mutation, JAK2V617F, which resulted in constitutive JAK2 signaling, was causative for PV, and the disease is, indeed, the ultimate phenotypic consequence of the JAK2V617F mutation. It was later shown, however, that the JAK2V617F mutation could arise in the PV hematopoietic stem cell as a secondary event,² and it was also found that the involved hematopoietic stem cell was not affected by JAK2 inhibitors.³ Interestingly, it was later shown that leukemic transformation in JAK2V617F-positive PV patients can occur in a JAK2V617F-negative clone.⁴ These observations prompted analyses directed toward better understanding of the biology of the PV initiating stem cell and toward determining additional factors involved in PV pathogenesis. Our group showed that sex, age at diagnosis and disease duration influenced the JAK2V617F allele burden. PV was found to be more common in women, who, compared to men, acquired PV at a younger age, had lower neutrophil counts, lower JAK2V617F allele burdens in the CD34+ cells, more splenomegaly and a much higher incidence of hepatic vein thrombosis.⁵ It was also shown that early in the disease course, the mean CD34+ cell JAK2V617F allele burden was lower than in the neutrophils.⁶ In addition, JAK2 wild-type CD34+ cells were still present when the JAK2V617F allele burden was lower in CD34+ cells than in neutrophils, but were not present in PV subjects in whom the JAK2V617F allele burden was similar between CD34+ cells and neutrophils.⁷ Clonal dominance, defined as the coherence between the JAK2V617F allele burdens of the CD34+ cells and the neutrophils, was present in more than 50% of PV patients, and was independent of the CD34+ cell JAK2V617F genotype (heterozygous or homozygous). Clonally dominant PV patients had a significantly longer disease durations, higher white cell counts and larger spleens than non-clonally dominant PV patients.⁷ These data pointed to a CD34+ cell as the cell responsible for initiation of PV. Using the activity of the enzyme aldehyde dehydrogenase (ALDH), which is known to be high in the CD34+CD38[−] cells, it was found that these cells were the initiating stem cell in PV. It was also found that ALDH activity was reduced in the CD34+CD38[−] blast cells of PV patients who had developed acute myeloid leukemia (AML). Furthermore, in some JAK2V617F-positive PV patients who developed AML, the CD34+

CD38[−] AML cells with reduced ALDH activity were also found to be JAK2V617F-negative. These data indicate that the cell involved in the initiation of PV is a primitive CD34+CD38[−] stem cell with high ALDH activity, and that AML arising in PV usually involves this cell but not always with expression of JAK2V617F.⁸ Finally, controlling for sex as a confounder, gene expression profiling of PV CD34+ cells identified a core set of 102 genes that were concordantly deregulated by both men and women PV patients and, thus, could be fundamentally involved in PV pathogenesis. Using different clustering algorithms, these core genes consistently divided PV patients into two groups: those with an aggressive form of the disease and those with indolent form independently of the JAK2V617F allelic burden. As few as 10 genes could be used to separate patients with aggressive disease from those with indolent disease, providing a CD34+ cell assay that could be useful in risk prognostication, as disease behavior in PV is CD34+ cell-dependent but not JAK2V617F allele burden-dependent.⁹

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