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A specific test for polycythemia vera?

Distinguishing between polycythemia vera (PV) and other polycythemic disorders can be very challenging. Although the diagnosis of PV may be straightforward if patients have the classic criteria as defined by the Polycythemia Vera Study Group, often patients present with an incomplete phenotype. Thus, a simple, readily available laboratory test to establish a diagnosis of PV would be highly desirable. In this issue, Klippel and colleagues (page 3569) report the utility of polycythemia rubra vera-1 (PRV-1) mRNA quantification in granulocytes for discrimination of PV from other polycythemias. The authors also report that PRV-1 may be overexpressed in the neutrophils of some patients with thrombocythemia and idiopathic myelofibrosis; it remains to be established if some patients presenting with a thrombocythemia phenotype may in fact be early PV, as reported by Shih et al,[1] and if those with PRV-1–positive idiopathic myelofibrosis have the spent phase of PV. These investigators have previously reported increased PRV-1 mRNA in PV granulocytes but not in their progenitors. The function of PRV-1 in normal hematopoiesis is unclear, as the amount of this protein does not differ between normal and PV cells.

However, quantification of PRV-1 mRNA may be a useful and specific diagnostic marker of PV. In PV, the EEC assay (endogenous erythroid colonies grown in in vitro cultures without erythropoietin) is specific in experienced hands, but it is not easy to standardize; it is labor intensive and requires expensive reagents. Similarly, assays of the clonality of circulating myeloid cells can be performed only in females, and not every female is informative for the X-chromosome-inactivation–based clonality studies. Other newly described PV abnormalities, such as platelet c-Mpl expression, are difficult to perform and available only in specialized laboratories. In contrast, the PRV-1 test is conceptually simple, has minimal inter- and intra-assay variation, and any competent laboratory equipped with the increasingly widely available real-time polymerase chain reaction (PCR) instrument should be able to perform it. However, occasional patients with congenital polycythemia[2] and familial thrombocytosis[3] were reported to have elevated PRV-1 levels, raising questions about its specificity. Thus, the usefulness and specificity of the PRV-1 test for PV diagnosis remain to be proved in prospective studies. However, due to its simplicity, the PRV-1 assay is attractive and it eventually may become the preferred PV test for all practicing hematologists.

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Mystery of thiamine-responsive megaloblastic anemia unlocked

Megaloblastic changes in the bone marrow are morphologically quite distinctive, and the several causes of this condition, including specific nutrient deficiencies, metabolic errors, and certain drugs, are well described. The underlying biochemical mechanisms responsible for these conspicuous changes are, however, not very well defined and remain somewhat speculative and controversial. There are basically 2 current theories, both rooted in the concept that nucleotide synthesis is impaired and that in folate and cobalamin (vitamin B_{12}) deficiency, at least, there is a critical lack of thymidine formation from deoxyuridine (dU) leading to catastrophic collapse of orderly DNA synthesis and repair.

In one theory, lack of deoxythymidine triphosphate (dTTP) retards the elongation of newly formed replicating segments of DNA, resulting in fatally fractured pieces that trigger premature apoptosis.[1] In the other theory, build-up of deoxyuridine triphosphate (dUTP) resulting from failure of conversion of dU to thymidine causes an inordinate accumulation of dUTP, which can then substitute for missing dTTP in the machinery of DNA polymerase activity. Misincorporation of dUTP results in excision of the faulty segment followed by misrepair while the famine for dTTP persists, and thus ensues a futile cycle of excision-misrepair.[2] This, too, results in apoptosis, the final common pathway of ineffective hematopoiesis in megaloblastic anemia.[3]

Among the more obscure causes of megaloblastic anemia is the acronymic curiosity thiamine-responsive megaloblastic anemia (TRMA), subject of an article by Boros and colleagues (page 3556). The use of mass spectrometry in conjunction with stable isotope-labeling techniques has made it possible to unlock doors along previously inaccessible hallways of gene function analysis in the metabolomic maze. The door to TRMA was thus opened by Boros et al, who have pioneered the use of stable isotope-based dynamic metabolic profiling (SIDMAP) as a key to better understanding of changes in substrate flow as a basis for drug mechanisms and disease. Teaming up with the Boston group who first identified the loss of function mutation in the high-affinity, low-capacity thiamine transporter in TRMA, the authors have pinpointed the cause of disruption of nucleic acid synthesis that leads ultimately to premature apoptosis in this intriguing genetic disorder.

Through tracking the stable ^{13}C-labeled glucose in fibroblasts from patients with TRMA, these authors concluded that the underlying lesion in this condition resides in