inside blood

$p21^{CIP1/WAF1/SDI1}$ hypermethylation: an exciting new lead in ALL biology

Roman-Gomez and colleagues (page 2291) have examined hypermethylation of the $p21^{CIP1/WAF1/SDI1}$ gene promoter in bone marrow cells from a large group of children and adult patients with acute lymphoblastic leukemia (ALL). Hypermethylation, observed in 51 of 124 patients, correlated strongly with decreased p21 mRNA levels and was highly predictive of a poor clinical outcome. Importantly, p21 hypermethylation was a significant independent prognostic factor for disease-free survival in both childhood and adult ALL. In fact, as a prognostic factor, p21 hypermethylation was fully comparable to, or even surpassed in predictive power, such long-established ALL risk factors as age, white blood cell count, or BCR-ABL expression.

Even though molecular abnormalities involving other cell-cycle regulatory genes, especially those encoding the INK4 proteins, are commonly encountered in ALL, clear correlations of these abnormalities with clinical or biologic behavior of the disease have been elusive. Therefore, the striking effect of p21 methylation status on the biology of ALL as revealed by Roman-Gomez et al's studies is quite novel and has major implications for both basic and clinical research in ALL. First is the possibility that p21 may play a uniquely important role in regulating the proliferation of ALL cells, which consequently may enjoy a growth advantage when p21 expression is blocked. Second, this consideration should encourage more intensive evaluations of agents that inhibit DNA methylation for the treatment of ALL. Third, if these observations are confirmed by other studies, p21 methylation status could be used as a stratification tool to provide effective risk-adapted therapy for ALL, a need that is especially acute for adults with this disease. Because of the tight correlation between p21 methylation status and mRNA levels, it is highly plausible to expect that a simple clinical laboratory test like immunocytochemistry might one day be used to screen new ALL cases for p21 expression and to provide meaningful risk stratification.

More work needs to be done: the authors point to the tantalizing association of coexisting hypermethylation of the p73 gene promoter, the role of histone deacetylation must be fully explored, and an alternative mechanism to hypermethylation for p21 silencing remains to be elucidated. But even with so many unanswered questions, it is intriguing to consider the many directions this exciting new lead in ALL biology may eventually take us.

—David H. Boldt
University of Texas Health Science Center at San Antonio