For the past three decades, researchers have been studying the interactions between hematopoietic stem cells and the surrounding cells of the bone marrow. The area where these interactions occur is called the hematopoietic microenvironment.1 Such interactions are key to the maintenance of hematopoietic stem cells and do not occur randomly in the bone marrow cavity; instead, they are preferentially located in different places within this space — hence the phrase “stem-cell niche.”2 A stem-cell niche is an accumulation of hematopoietic stem cells in a particular place that sustains the survival and function of the cells through cell–cell and cell–matrix interactions. A recent study by Iwamoto and colleagues3 defines a biochemical aspect of this bone marrow microenvironment that may be important in the therapy of acute lymphoblastic leukemia (ALL).

Increasingly, it appears that, like hematopoietic stem cells, leukemic stem cells — those cells responsible for the maintenance and resurgence of leukemia after elimination of the bulk of the leukemic blasts — interact with nonhematopoietic cells of the bone marrow microenvironment. For example, the leukemic cells of ALL and of chronic myelogenous leukemia interact with the hematopoietic microenvironment through multiple cell–surface proteins, including CD44. Blocking CD44, which has been implicated in normal hematopoietic stem-cell adhesion, abrogates these interactions and delays the progression of leukemia in mouse models of the disease.4

Iwamoto et al. extend our understanding of the “leukemic stem-cell” niche. They show that stromal cells (also called mesenchymal cells) generate and secrete large amounts of asparagine synthetase, an enzyme that is critical to the biosynthesis of the essential amino acid, asparagine. They do not determine how asparagine synthetase is relevant to the biology of ALL, but the therapeutic implications are evident to anyone who has cared for children with this disease. Asparaginase, which depletes cells of asparagine, has been used to treat ALL for many years, and it contributes considerably to the improved outcome now seen in the treatment of this disease. Clinical studies have shown a direct relationship between the outcome in ALL and the dose intensity of treatment with asparaginase.5 However, the mechanism underlying the failure of and resistance to asparaginase treatment has been obscure.

Iwamoto et al. hypothesized that the interaction between leukemic blasts and bone marrow mesenchymal cells might provide a “protective” environment for ALL blasts against asparaginase treatment. With the use of gene arrays and then biochemical assays, they showed that bone marrow mesenchymal cells express significantly higher amounts of asparagine synthetase than do leukemic blast cells (Fig. 1). They then showed that the resistance of leukemic cell lines and some specimens of primary leukemia to asparaginase is correlated with the expression of asparagine synthetase by mesenchymal cells. Manipulation of asparaginase synthetase activity in a given mesenchymal cell line (either by overexpression or knockdown) results in the predicted effect on asparaginase sensitivity. That is, increased expression of asparaginase synthetase by the mesenchymal cell leads to increased resistance of the ALL cells; conversely, reduced expression of asparaginase synthetase by the mesenchymal cell leads to enhanced sensitivity of the ALL cells.

The authors did not show that this association is critical in vivo and that the relationship between leukemic cells and the mesenchymal cell holds for minimal residual disease in ALL. Whether there is a true leukemic stem cell in this disease is open to debate. A therapeutic application would also require the development of appropriate techniques to target the reduction of asparagine synthetase in the bone marrow microenvironment. Thus, there is grist for the research mill; this grist must be ground before we will know whether this new discovery3 can be translated into new therapies. However, one can envision that targeting the ALL cell
by reducing the expression of asparagine synthetase by the bone marrow mesenchymal cell may well improve the outcome in patients with new disease and in those with relapsed disease.

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