To the editor:

Is hematopoietic stem cell homing deficient in Fanconi anemia?

We read with interest the article by Zhang and colleagues comparing progenitor colony formation, chimerism after xenotransplantation into immunodeficient mice, and adhesive properties of whole bone marrow (WBM) cells from Fanconi anemia (FA) patients and healthy donors.1 We applaud the study of this important topic, but would caution that assays of clonogenicity and hematopoietic repopulation are not sufficiently specific measures of homing. In fact, both are inherently skewed by the complex phenotype of FA hematopoietic stem cells (HSCs), comprising exaggerated apoptotic responses, constitutive cell-cycle arrest, pronounced sensitivity to reactive oxygen species, and reduced replicative fitness.2,3 Furthermore, the ability of cells to home to the microenvironment is an attribute of primitive cells. Experimental observations in WBM cells or immortalized lymphoblasts are not always faithful reflections of stem and progenitor cell behavior.4 For example, the expression of chemokine receptor 4 (CXCR4), a key homing molecule, is selectively increased in highly enriched sca+, c-kit+, lin− (SKL) progenitors, but not in WBM from C57Bl/6 wild-type and Fancc−/− mice, a murine model of FA (Figure 1A). Indeed, we previously demonstrated only modest differences in steady-state or induced CXCR4 expression and in vitro migration among lin− progenitors from Fancc−/−, c−/−, -d2/−, and wild-type animals. Cell-surface CXCR4 expression in wild-type and Fancc−/− genotypes, respectively, was up-regulated by culture at low (1%) oxygen concentration and promoted hematopoietic engraftment.5

By comparison with repopulation studies, adhesion assays provide a much more restrictive measure of cellular function and our experiments in Fancc−/− and wild-type WBM cells confirm the deficiency in cell-matrix adhesion observed by Zhang et al in FA patient WBM cells (Figure 1B). The authors associate this phenotype with reduced cdc42 activity in FA lymphoblasts. However, others previously showed that latent Epstein-Barr virus (EBV) membrane protein 1 activates cdc42 through a mechanism that mimics tumor necrosis factor α activity.6 Could discrepant cdc42 activity be related to differential responses by FA cells to EBV immortalization? Cell type–specific effects of cdc42 inactivation not only impact adhesion, but also promote cell-cycle acceleration as well as increases in progenitor frequency and clonogenicity.7 How can this be reconciled with the FA-specific G2 arrest, reduced colony formation, and poor progenitor mobilization?8,9

It is tempting to conclude that defective adhesion of FA WBM cells and decreased cdc42 activity in FA lymphoblasts imply deficient homing. A systematic, cell type–specific analysis may yet reveal such deficiencies, but the data by Zhang do not provide specific evidence for defective homing, nor a direct correlation with cdc42 activity in FA-HSC. By contrast, regulation of CXCR4 in enriched progenitors from Fancc−/− mice appears intact and, if confirmed in patient cells, could be therapeutically exploited to offset repopulation deficits.5,8 Much like an appreciation of FA protein involvement in DNA repair has produced general insight into molecular mechanisms of cancer, a nuanced evaluation of HSC deficiencies stands to yield broadly applicable gains in understanding hematopoietic failure.

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