levels, potentially allowing the use of lower, clinically acceptable vector doses. The simultaneous development of different gene therapy approaches is justified to bring a cure for hemophilia A one step closer to reality.

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Fanconi anemia stem cells: going round and round

Fanconi anemia (FA) is a congenital form of aplastic anemia and is transmitted through an autosomal recessive mode. Inactivation of any of the 7 FA genes leads to progressive bone marrow (BM) failure, congenital abnormalities, and a predisposition to malignancy. Since a defect in any of the FA genes leads to a similar clinical phenotype, FA proteins appear to act together physically and functionally in a common pathway. However, the question remains: What role does each FA protein or the FA complex play in hematopoiesis?

Studies using the FA group C mouse model have shown that *Fancc*$^{-/-}$ hematopoietic stem cells have impaired function shown by reduced repopulating ability and are found at lower numbers in *Fancc*$^{-/-}$ BM. These results and the fact that BM aplasia in patients with FA is progressive suggest that the FA gene products are required for the maintenance of normal numbers of stem cells and/or for normal stem cell development.

In this issue, Li and colleagues (page 2081) have defined a new phenotype associated with *Fancc*$^{-/-}$ stem cells. Using 2 simple assays, these authors have evaluated the cycling state of the hematopoietic stem/progenitor cell fraction from *Fancc*$^{-/-}$ mice. They show that the stem/progenitor-enriched fraction is less quiescent than wild-type (WT) controls showing more bromodeoxyuridine (BrdU) incorporation and fewer cells in G0. They go on to show that the altered cell cycle kinetics in *Fancc*$^{-/-}$ cells are, at least in part, cell autonomous and do not result from unscheduled DNA synthesis or increased damage and repair. In addition, the increased cycling activity found in *Fancc*$^{-/-}$ hematopoietic cells does not seem to be a compensatory response related to their proapoptotic phenotype but may indeed contribute to the increased apoptotic response of these cells to cytokines. On the other hand, the defect in cytokine signaling in *Fancc*$^{-/-}$ hematopoietic cells may contribute to the increased cycling activity. In any case, Li and colleagues clearly demonstrate that an accelerated cycling rate in *Fancc*$^{-/-}$ cells, whether a direct or indirect consequence of absence of the *Fancc* gene, is a contributing factor to stem cell exhaustion in FA leading to BM failure.

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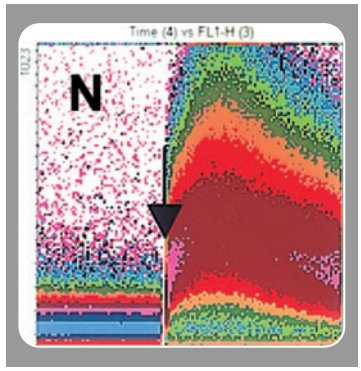
CD38: what is it there for?

CD38 is very much a molecule of the moment. Since it has been mentioned in well over 1000 articles in the past 5 years, we are entitled to ask, "What is it there for?" It is a type II transmembrane glycoprotein, the extracellular domain acting as an ectoenzyme, catalyzing the conversion of nicotinamide adenine dinucleotide (NAD^+) into nicotinamide, adenosine diphosphate–ribose (ADPR), and cyclic ADPR. CD38 is expressed on many types of cells, but recent interest focuses on its role on B lymphocytes. Its expression during B-cell ontogeny is tightly regulated: it appears on bone marrow precursor cells but is lost on mature lymphocytes; on germinal center cells it protects against apoptosis, but on leaving the germinal center, memory cells lack the antigen; on terminally differentiated plasma cells it is one of the few surface antigens present. In chronic lymphocytic leukemia (CLL), expression of CD38 signifies a poor prognosis, though it does not correlate precisely with the presence of unmutated immunoglobulin variable region (*IgV*) genes and may vary during the course of the disease.[1]



Is it more than a prognostic marker? Deaglio and colleagues (page 2146) suggest that CD38 is involved in signaling through the B-cell receptor (BCR). Unfortunately, even $CD38^+$ CLL cells express the molecule at such low density that few cells show detectable signals on ligation by antibody. However, when the expression of CD38 was upregulated by exposing the cells to interleukin 2 (IL-2), incubation with anti-CD38 antibodies mediated a signal that could be detected by Ca^{++} flux. Because CD38 patches on the