Stem cell damage, adaptation, and leukemogenesis in Fanconi anemia

Biallelic inactivation of any one of 7 genes results in Fanconi anemia (FA), a rare disease that predisposes children and adults to bone marrow failure, endocrinopathies, myelodysplasia (MDS), acute myelogenous leukemia (AML), and epithelial malignancies. There exists evidence that the FA proteins participate together physically and functionally in the nucleus to effect one or more types of DNA repair pathway. Equally strong is evidence that the FA proteins are multifunctional and participate independently in survival signaling pathways in hematopoietic cells (mutant cells are proapoptotic). What role does failure of each of these functions play in outgrowth of leukemic clones?

In this issue, Haneline and colleagues (page 1299) tackle this question and resolve 4 unanswered questions about murine models of FA. First, can one develop a model of marrow failure without exposing the mice to alkylating agents? Yes, by transplanting stem cells of *Fancc* knockout mice into lethally irradiated recipients. Second, are stem cells as hypersensitive to extracellular apoptotic cues? Yes. Stem cells of the Fancc$^{-/-}$ mice were intolerant of ex vivo manipulation. Third, do mice show suggestive evidence of clonal adaptation, MDS, or AML? Yes. Some of the mice with low levels of chimerism later developed increasing fractional repopulation by the mutant cells and their progeny were resistant to apoptotic cues ex vivo. Fourth, do mice receiving transplants of mutant stem cells corrected by a *Fancc*-expressing retroviral vector develop hematopoietic defects? Yes, but at a rate much lower than that of the mice receiving uncorrected cells. Implication? Gene therapy may not only fix the bone marrow failure syndrome in FA patients but prevent MDS and AML as well. Clearly, many questions remain for us all to tackle, but Haneline and her group should be congratulated for solving so many problems in this field with one carefully done study.

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PS-341: prospecting a new hope for myeloma

In this issue, Hideshima and colleagues (page 1530) define the intracellular effects of the proteasome inhibitor PS-341 (Millennium Pharmaceuticals, Cambridge, MA) on myeloma cells. This drug has shown promising activity in early clinical trials for relapsing myeloma patients. Moreover, recent laboratory studies show that exposure to this agent may greatly increase the sensitivity of highly chemotherapy-resistant myeloma cells to the cytotoxic effects of chemotherapy, and have led to clinical trials exploiting this effect for myeloma patients. PS-341 reduces the DNA-binding activity of the transcription factor nuclear factor-kappa B (NF-κB) by reducing the degradation of the NF-κB inhibitor, IκB. In support of this, expression of a dominant-negative vector of IκB that is resistant to proteasome-mediated degradation induces apoptosis in both chemotherapy-sensitive and -resistant myeloma cells.

But recent studies, including the Hideshima paper, suggest that other effects of PS-341 may contribute to its antimyeloma effects. This drug has profound effects on TNF, JNK activities, p53, MDM2, DNA protein kinase catalytic subunit (DNA-PKcs), and the ATM proteins. Specifically, exposure to this drug inhibits *XIAP*, a gene activated by NF-κB. This results in enhanced JNK activity, leading to caspase-mediated apoptosis. Other studies have shown that the enhancement of JNK activity by PS-341 is associated with increased TNF production. Indeed, inhibition of TNF reduces the antitumor effects of PS-341. Moreover, this induction of JNK activity also results in activation of caspase-3, leading to cleavage of DNA repair enzymes including DNA-PKcs and ATM, resulting in impaired DNA repair. The proteasome inhibitor also increases p53, resulting in induction of MDM2 expression, as well as enhanced association of these 2 proteins. Ultimately, the activation of caspase-3 leads to p53 phosphorylation and MDM2 degradation, resulting in activation of p53. Thus, the proapoptotic activities of PS-341 on multiple intracellular signaling pathways in myeloma cells results in its potent antitumor effects.

Importantly, furthering our understanding of the intracellular antimyeloma effects of PS-341 will help lead to the development of other drugs that more specifically target these pathways and the exploration of new drug combinations with the potential for enhanced clinical benefits.

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Urokinase mediates receptor cross-talk

Cell-cell and cell-matrix interactions are key events in inflammatory cell reactions or during tissue remodeling. For cellular migration or invasion to occur, both integrin adhesion receptors and proteolytic systems linked to the cell surface are required. Here, the urokinase (uPA) receptor plays a central role: It can concentrate its ligand uPA and concomitant plasmin formation within the pericellular space and can also regulate integrin function by direct physical interactions. Although (enzymatically inactive) uPA was known also to induce cellular responses of cells lacking the glycolipid-anchored uPA receptor, a conclusive mechanistic explanation for these activities was missing so far.

Pluskota and colleagues (page 1582) have now identified the major β_2 integrin on neutrophils, Mac-1, as an additional receptor for uPA, and present conclusive evidence that the kringle and protease domains of the "new" ligand uPA are recognized by the I-domain of this integrin. Mac-1 thereby becomes an even more crowded multifunctional recognition platform, particularly on neutrophils or monocytes: besides binding