Y-chromosome–encoded dead box RNA helicase Y (DBY) protein by Western blot analysis and enzyme-linked immunosorbert assay (ELISA) techniques. They found antibodies against DBY in 50% of male patients who received stem cell grafts from female donors. The same antibodies were detected in about 15% to 20% of healthy females, but were not found in healthy males. Antibody responses were primarily directed against areas of amino acid disparity between DBY and its female homologous counterpart DBX. Clearly, the Y-linked DBY protein can trigger a B-cell–mediated immune response. Randolph and colleagues (page 347) analyzed 3238 individuals who received HLA-identical sibling HSC transplants for various hematologic malignancies. Transplantation-related mortality is more of a concern than rejection. In the past, the strategy was clear: a female donor for a male recipient was to be avoided. The decision has now become more difficult. In the short term, survival is worse for males with female grafts. The detrimental effect of GVH reaction is, early after HSCT, higher than the benefit from GVL. However, if with longer follow-up the GVL benefit outweighs early loss, we might have to reconsider the decisions of today.

The findings raise even more intriguing questions. What are the mechanisms behind the recognition of male gene products by women? If nearly 20% of healthy women and 50% of male recipients of female transplants have anti-Y antibodies, why are the clinical consequences so rare? Why are so many HLA-identical sex-mismatched transplants accepted with no rejection? Why are male fetuses safe during pregnancy? There is a hint to these questions in the work of Miklos et al. In all situations when they were able to identify the peptide sequences, there was a difference between the male DBY and female DBX protein. It is unknown whether the differences in these peptides represent spontaneous mutations or a basic inherent sex-linked difference. Obviously, we received clear answers but are left with many open questions.

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Myeloma is on the move

Mature plasma cells and myeloma cells migrate to the bone, and myeloma cells have the ability to metastasize to different bone marrow and extramedullary sites. Although macrophage inflammatory protein 1α and monocyte chemoattractant protein 1 have been shown to induce migration of myeloma cells, and other chemokines and chemokine receptors have been implicated in myeloma cell movement, the mechanism(s) by which these cells move are not completely understood. In this issue, Qiang and colleagues (page 301) provide compelling evidence that insulin-like growth factor-1 (IGF-1), an already established growth and survival factor for myeloma in vitro, is also an inducer of myeloma cell migration.

Interest in IGFs and their effect on carcinogenesis has increased recently because high IGF-1 serum concentrations are associated with an increased risk of breast, prostate, colorectal, and lung cancers. Indications are that IGF-1 also plays a role in myeloma. In a recent case report, the conversion of monoclonal gammopathy of undetermined significance to overt myeloma occurred in strict temporal relationship with elevated serum IGF-1 levels. In addition, serum IGF-1 levels have been linked to survival in myeloma. We have shown that IGFR is the only gene significantly elevated in a comparison of microarray profiles of myeloma cells with and without chromosome 13 deletion, a dire prognostic feature, and more recent analysis has revealed that elevated expression of IGFR is associated
with an increased risk of mortality in myeloma patients treated with tandem stem cell transplants (our unpublished data, May 2003).

Ge and Rudikoff were the first to show that virtually all myeloma cell lines express IGF1R, and that ligand binding causes activation of phosphatidylinositol-3’-kinase (PI-3K), which in turn increases survival and proliferation. Ge NL, Rudikoff S. Insulin-like growth factor I is a dual effector of multiple myeloma cell growth. Blood. 2000;96:2856-2861.

IGF-1 activates Akt and Bad, leading to apoptosis inhibition, and mitogen-activated protein kinase (MAPK), resulting in proliferation. Although Vanderkerken and colleagues have previously shown that IGF-1 is a bone marrow–derived chemoattractant for myeloma cells in the 5T2 model, Vanderkerken, Asosingh K, Braet F, Van Riet I, Van Camp B. Insulin-like growth factor-1 acts as a chemoattractant factor for 5T2 multiple myeloma cells. Blood. 1999;93:235-241.

In an independent study, Tai et al have shown that IGF-1 stimulates migration, but, in their hands, this is Akt-dependent. Tai YT, Podar K, Catley L. Insulin-like growth factor-1 induces adhesion and migration in human multiple myeloma cells via activation of beta1-integrin and phosphatidylinositol 3’-kinase/AKT signaling. Cancer Res. 2003;63:5850-5858.

An important biologic question raised by Qiang and colleagues is how can IGF-1 induce proliferation and migration? The authors have put forth an intriguing model suggesting that local concentration gradients of IGF-1 determine whether a given cell will migrate or will proliferate. Ge NL, Rudikoff S. Insulin-like growth factor I is a dual effector of multiple myeloma cell growth. Blood. 2000;96:2856-2861.

The IGF-1 signaling cascade continues to be implicated in several aspects of myeloma biology and, as such, must be seriously considered as a potential new therapeutic target in this difficult-to-manage cancer.

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Myeloma is on the move

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