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## Myeloma is on the move

John D. Shaughnessy, Jr

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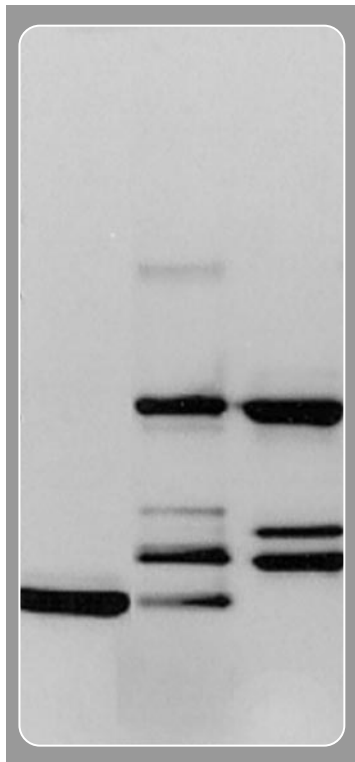
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Y-chromosome–encoded dead box RNA helicase Y (DBY) protein by Western blot analysis and enzyme-linked immunosorbent assay (ELISA) techniques. They found antibodies against DBY in 50% of male patients who received stem cell grafts from female donors. 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 and looked at incidence of GVHD and relapse. GVHD was, as expected, higher in male recipients of female grafts. The same recipients did exhibit a lower hazard of relapse compared with other sex combinations. This graft-versus-leukemia effect (GVL) was preserved even after controlling for GVHD as a time-dependent covariate.

Hence, Y-antigen–encoded gene products can act as minor histocompatibility antigens and trigger rejection, GVHD, and GVL. These Y-chromosome–associated effects reflect the full repertoire of the immune response.

These observations have direct clinical consequences. Donor-recipient sex combination has to be considered in any donor-selection algorithm. Rejection is primarily of concern when transplantation is planned for aplastic anemia or congenital disorders. If there is a choice, a male donor for female recipient should not be selected. The decision is more complex in 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.<sup>4</sup> 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.

—Alois Gratwohl  
Kantonsspital Basel

1. Uphoff DE. Comparative survival of lethally irradiated inbred male mice inoculated with marrow from virgin or multiparous female donors. *J Natl Cancer Inst.* 1975;54:1343-1347.

2. Spierings E, Vermeulen CJ, Vogt MH, et al. Identification of HLA class II-restricted H-Y-specific T-helper epitope evoking CD4+ T-helper cells in H-Y-mismatched transplantation. *Lancet.* 2003; 362:610-615.
3. Zwaan FE, Hermans J, Gratwohl A, for the EBMT Leukaemia Party (EBMT-LWP). The influence of donor-recipient sex mismatching on the outcome of allogeneic BMT in leukemia. *Bone Marrow Transplant.* 1989;4(suppl 2):8.
4. Gratwohl A, Hermans J, Goldman JM, et al, for the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. *Lancet.* 1998;352:1087-1092.

## 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 1  $\alpha$  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.<sup>1</sup> In addition, serum IGF-1 levels have been linked to survival in myeloma.<sup>2</sup> We have shown that *IGF1R* 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,<sup>3</sup> and more recent analysis has revealed that elevated expression of *IGF1R* 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.<sup>4</sup> 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,<sup>5</sup> in this issue, Qiang, Rudikoff, and colleagues show that IGF-1 mediates cell migration of human myeloma cells and that this is dependent on RhoA signaling. Interestingly, this same group has recently shown that a Wnt3A-induced shift in cell morphology is also RhoA-dependent.

In an independent study, Tai et al have shown that IGF-1 stimulates migration, but, in their hands, this is Akt-dependent.<sup>6</sup> Tai et al<sup>6</sup> and Qiang et al used different myeloma cell lines, which may account for the divergent findings of Akt involvement in IGF-1-induced cell migration. Given the molecular

and clinical heterogeneity of myeloma, these differences could reflect molecular variation in the tumors from which the cell lines were originally derived. Alternatively, the disagreement may be explained by subtle differences in the experimental conditions or genetic changes that occurred in long-term cell cultures. Nevertheless, these discrepancies point to the potential problems of extrapolating data from cell lines to primary tumor biology. Data derived from cell lines must be interpreted with caution as these models are typically derived from end-stage disease and may use signaling pathways that are not relevant to primary tumor biology. Thus, it will be important to determine if primary isolates respond to IGF-1, if IGF-1 induces migration through RhoA and/or Akt, and, if this heterogeneity is confirmed, if it correlates with clinical features of the disease.

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.

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.

—John D. Shaughnessy Jr

Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences

1. Tucci A, Bonadonna S, Cattaneo C, Ungari M, Giustina A, Guiseppe R. Transformation of a MGUS to overt multiple myeloma: the possible role of a pituitary macroadenoma secreting high levels of insulin-like growth factor 1 (IGF-1). *Leuk Lymphoma*. 2003;44:543-545.
2. Standal T, Borset M, Lenhoff S, et al. Serum insulin-like growth factor is not elevated in patients with multiple myeloma but is still a prognostic factor. *Blood*. 2002;100:3925-3929.
3. Shaughnessy J, Jacobson J, Sawyer J, et al. Continuous absence of metaphase-defined cytogenetic abnormalities, especially of chromosome 13 and hypodiploidy, ensures long-term survival in multiple myeloma treated with Total Therapy I: interpretation in the context of global gene expression. *Blood*. 2003;101:3849-3856.
4. Ge NL, Rudikoff S. Insulin-like growth factor I is a dual effector of multiple myeloma cell growth. *Blood*. 2000;96:2856-2861.
5. Vanderkerken K, 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.
6. Tai YT, Podar K, Csatly 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.