and eosinophils in the pathogenesis of severe disease pathology associated with IHES.

These results clearly open up several new major areas for research investigation. In particular, it will be critical to determine the molecular explanation for the association of tryptase with IHES. This association may be explained by the ability of aggressive eosinophils to stimulate mast cells, or alternatively, the FIP1L1-PDGFRA fusion protein may participate in multiple hematopoietic lineages, especially mast cells and eosinophils.

Before closing, a word of caution should be stated concerning nomenclature. While the authors refer to their patients as having "hypereosinophilic syndrome," this categorization is fairly broad and nonspecific since numerous disease entities (eg, Churg-Strauss syndrome and eosinophilic gastroenteritis) may be considered to be hypereosinophilic syndromes. My own preference, consistent with Cools et al, calls these patients IHES rather than HES. As such, IHES patients have a strong male-sex predominance (9:1 male-female ratio), and a high probability of the FIP1L1-PDGFRA fusion event, and imatinib responsiveness. The strong male-sex predominance in tryptase-positive IHES patients suggests the importance of X-linked modifying genes. Clearly, this study represents a large step forward in understanding the pathogenesis of IHES. The authors are to be congratulated for making this important contribution.

—Marc E. Rothenberg
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Progress with unrelated cord blood transplants in adults

In the 1980s, the idea that umbilical cord blood (UCB) contained sufficient hematopoietic stem cells to rescue myeloablated bone marrow was disregarded by most marrow transplanters. In 1989, when Gluckman and colleagues reported the successful transplantation into a 6-year-old boy with Fanconi anemia of HLA-matched cord blood from his baby sister (Gluckman et al, N Engl J Med. 1989;321:1174-1178), many thought that the substitute of this unique stem cell source would only have utility in children. This perception was reinforced in 1996 when the results of the first 25 unrelated, partially HLA-mismatched transplantations performed between 1993 and 1995, with units from the public bank established by Dr Pablo Rubinstein, demonstrated a 48% event-free survival, again in children (Kurtzberg et al, N Engl J Med. 1996;335:157-166). In these early studies, cord blood was shown to cause less acute and chronic graft-versus-host disease than did better-matched adult stem cells, stimulating the use of mismatched unrelated cord blood transplantation in patients lacking matched donors. In follow-up, the first UCB transplant recipient, as well as 11 of the 12 survivors of the first 25 unrelated transplantations, originally reported in 1996, are currently in good health with 100% donor chimerism.

Reports over the next 5 years from single institutions and various registries observed that the cell dose delivered by the cord blood unit influenced engraftment and overall survival. Given that adults are larger than children, there was limited enthusiasm for use of cord blood in adults and the limited retrospective trials performed in the United States demonstrated inferior outcomes, due in large part to selection of patients with end-stage disease receiving low (fewer than 2×10^7 cells/kg) cord blood cell dosing (Laughlin et al, N Engl J Med. 1002;344:1815-1822). The study by Ooi and colleagues in this issue (page 4711) provides the first encouraging results in adults receiving transplants of unrelated cord blood.

What is different? Cell dosing! It appears that cord blood dosing approaches the threshold necessary for engraftment. When dosed with adequate numbers of cells (in this report a median of 2.43×10^7 cells/kg), a group of very high–risk patients can demonstrate superior survivals. The authors should be congratulated for their perseverance in testing and contributing to our understanding of this promising stem cell source.

—Joanne Kurtzberg
Duke University Medical Center

New targets for antiadhesion therapy of human multiple sclerosis

Multiple sclerosis (MS) is a debilitating inflammatory disease of the central nervous system (CNS). There has been a lot of interest in the use of antiadhesion molecule therapy to prevent the recruitment of inflammatory cells to the CNS, thereby attenuating disease. Based on observations that blockade of α_4 integrin was beneficial in animal models of MS, interest has focused exclusively on this molecule in the treatment of human patients, and clinical trials are now under way (Miller et al, New Engl J Med. 2003;348:15-23). Promising initial results have provided an impetus for exploring other antiadhesion pathways.

The P-selectin–PSGL-1 pathway is extremely effective at tethering various leukocytes to the vessel wall, particularly at the high shear rates found in the CNS. Despite this, a role for P-selectin in MS has been largely dismissed, based on observations that selectin blockade alone had no apparent effect on the clinical development of a murine model of MS (Engelhardt et al, Blood. 1997;90:4459-4472). But by visualizing the cerebral microvasculature using intravital microscopy, a number of groups have identified a critical role for P-selectin or its ligand, PSGL-1, in the recruitment of leukocytes to the CNS in a number of models of inflammation, including a model of MS (Piccio et al, J Immunol. 2002;168:1940-1949; Kerfoot and Kubes, J Immunol. 2002;169:1000-1006). Of course, some caution is necessary when one extends mouse data to human disease.

In this issue, Battistini and colleagues (page 4775) use a novel zoonotic approach to observe the recruitment of human leukocytes from MS patients to inflamed murine brain microvessels and, for the first time, demonstrate a possible role for the P-selectin

ligand PSGL-1 in human disease. In particular, the authors determined that $CD8^+$ T cells from MS patients were more prone to adhesion than $CD4^+$ T cells via predominantly a P-selectin–PSGL-1, and not an α_4 integrin–VCAM-1, pathway. An alternative approach to using LPS to induce P-selectin and VCAM-1 on the mouse brain microvessels would have been to induce experimental autoimmune encephalomyelitis. But the levels of these adhesion molecules are similar in these two models in our laboratory. Although the transmigration of these cells was not investigated, $CD8^+$ T cells are found in high numbers in active MS lesions, highlighting the potential benefit of including blockade of PSGL-1–P-selectin along with α_4 integin blockade in the treatment of MS. This paper reminds us of the complexity of MS, which includes the infiltration of multiple leukocyte subsets that almost certainly will have different adhesive profiles. Combination therapy blocking multiple pathways of recruitment (including the P-selectin–PSGL-1 pathway) may prove to be of greater benefit.

—Paul Kubes and Steven M. Kerfoot
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Factor XI inhibitors

Alloantibody inhibitors to factor VIII or factor IX are well-recognized consequences of replacement therapy in hemophilia. Factor replacement is also a mainstay of treatment for factor XI deficiency, but reports of factor XI inhibitors are anecdotal and few are well characterized. Factor XI deficiency is an autosomal disorder common in Ashkenazi Jews, in whom the prevalence of severe (homozygous) disease is 0.1% to 0.3%. Two mutations account for more than 90% of abnormal alleles in this population. Homozygosity for the type II (Glu117Stop) mutation is associated with the absence of factor XI antigen in plasma. This mutation is also found in Iraqi, Middle Eastern, and Sephardic Jews and in Arabs and probably arose in the Middle East at least 2000 years ago. The type III mutation (Phe283Leu) is likely of more recent European origin and is associated with reduced, but detectable, antigen (about 10% of normal in homozygotes). Compound heterozygotes for the 2 mutations have factor levels of about 3%.

In this issue, Salomon and colleagues (page 4783) report on inhibitor formation in 118 Israeli patients with severe factor XI deficiency. Seven individuals with histories of plasma infusion had inhibitors. All 7 are homozygous for the type II nonsense mutation. This group represents a striking 33% of all patients with this genotype exposed to plasma. Prospective studies of factor VIII inhibitors in hemophilia A indicate that many are transient, so the actual incidence of inhibitors in factor XI type II homozygotes exposed to plasma may be considerably higher than 33%. Given this, it seems prudent to prospectively identify these patients and, when possible, use alternatives to plasma therapy such as antifibrinolytic agents. Accurately measuring very low factor XI levels with clotting assays is notoriously difficult. This study points out the importance of determining factor XI genotype in Jewish patients to identify those at high risk for developing inhibitors.

—David Gailani
Vanderbilt University

Targeting DCs to induce regulatory T cells in vivo

Dendritic cells (DCs) play a central role in controlling immune responses, as initiators of either T-cell activation or tolerance. The functional activity of DCs, and thereby the outcome of an immune response, is determined in part by their maturation state. Immature (resting or steady-state) DCs may present antigen to T cells in a tolerogenic fashion, whereas mature (activated) DCs induce T-cell activation. Steinman and Nussenzweig proposed that immature DCs are crucial to the maintenance of immunologic self-tolerance (Proc Nat Acad Sci U S A. 2002;99:351-358). Tissue damage and/or inflammation induce maturation of DCs. In an inappropriate setting, this may lead to a break in tolerance to self-antigens and activation of autoreactive T cells.

Efforts to exploit the tolerogenic potential of immature DCs are being actively pursued. Hawiger and colleagues (J Exp Med. 2001;194:769-779) were the first to use antibody to DEC-205, a DC-restricted endocytic receptor, to specifically target antigen to immature DCs for tolerance induction in vivo. Antibody bound to DEC-205 is efficiently internalized and delivered to antigen processing compartments inside the cell (along with linked protein) without inducing DC maturation.

In this issue, Mahnke and colleagues (page 4862), using anti-DEC mAb linked biochemically to ovalbumin (OVA), report that tolerance induction in vivo is associated with an increase in $CD4^+$ $CD25^+$ regulatory T (T_{REG}) cells that coexpress $CTLA\text{-}4^+$. Subcutaneous injection of OVA-anti-DEC conjugates induced anergy in vitro and in vivo in OVA-specific TCR transgenic T-cells and also suppressed the OVA-specific DTH response in vivo. $CTLA\text{-}4^+$ $CD4^+$ $CD25^+$ T_{REG} cells were induced exclusively in OVA-anti-DEC–treated mice. $CD4^+$ $CD25^+$ TCR transgenic T cells recovered from these mice actively suppressed cytokine secretion and T-cell proliferation in vitro in a dose- and cell-contact–dependent manner; their depletion restored IL-2 production and T-cell proliferation. Coinjection of anti-CD40 mAb, a potent DC-maturation stimulus, abrogated the suppression of T-cell proliferation and restored IL-2 production as well as the DTH response to OVA, confirming the importance of the DC maturation state in activation of T_{REG} cells and tolerance induction in vivo.

Naturally occurring $CD4^+$ $CD25^+$ T_{REG} cells, together with other immunoregulatory cells, carry out an important physiologic function: the need to balance self-recognition and reactivity with self-tolerance. Anergic T cells can manifest functional properties similar to those of natural regulatory T cells, and immature DCs have been implicated in the induction of both anergic and regulatory T cells (Jonuleit et al, Trend Immunol. 2001;22:394-400). We are just beginning to tap the potential for manipulating and using