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.

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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.

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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