In this issue

By John Ashkenas, Science Editor

Bone defects in osteonectin-null mice

(See article on pages 915–923.)

The bone extracellular matrix (ECM) protein osteonectin, discovered independently in soft tissues (and often referred to as SPARC), is intriguing for its distribution and its diverse effects on cells in culture. This protein is present in multiple adult tissues and is induced early in development and in tissues undergoing remodeling. In bone, osteonectin binds collagen and hydroxyapatite, suggesting that it might help maintain the structure of bone ECM, and in other cell types it regulates cell shape, adhesion, and ECM remodeling. Targeted mutations that eliminate osteonectin expression cause a relatively mild phenotype with no obvious defects in bone form or size, but now Delany et al. report that bones from knockout animals are indeed affected in their interior structure and their mechanical properties. The effect of the mutation is seen most clearly in the reduction in trabecular tissue, spongy material that extends deep inside the bone and contributes to a long bone's strength and stiffness. Delany and colleagues find that absence of osteonectin suppresses the number of both bone-depositing osteoblasts and bone-resorbing osteoclasts. Because the former effect is more severe, a progressive loss of trabecular bone ensues, causing the bone to grow fragile. The relatively mild effects of the mutation are still striking, but the authors note that other related proteins, particularly the homologous protein SC-1, may compensate for the loss of osteonectin. SC-1 deficient animals were recently found to have a grossly normal phenotype, but the double mutant strain is not yet reported.

Eosinophils exit the lung and home to lymph nodes

(See article on pages 945–953.)

The transit of eosinophils from the bloodstream into the lung represents a key step in asthma pathogenesis, since these cells respond to allergens and secrete protein and lipid mediators of bronchial inflammation. For this reason, considerable interest centers on the molecular interactions that allow eosinophils to home to regions of inflammation within the tissue. As Shi et al. note, however, there has been little interest in the fate of eosinophils after they reach the lumen of the lung. To address this question, these authors prepared active eosinophils from the bronchoalveolar lavage of mice treated with one of several inhaled allergens. In cell culture, these eosinophils could activate antigen-specific T-cell responses, consistent with earlier evidence that eosinophils act as antigen-presenting cells (APCs) in vitro. Remarkably, within 8 hours of being transferred into the lungs of host animals, fluorescently labeled eosinophils could be seen in paratracheal lymph nodes, where $CD4^+$ T cells were activated that were specific for the antigen to which the eosinophils had been exposed. Thus, eosinophils can exit as well as enter the lung and can act as APCs in vivo. Shi et al. also argue that eosinophils' ability to phagocytose large particles suggests that they process particulate allergens and present epitopes that contribute to allergic reactions to particulate inhalants.

Bystander suppression of autoimmune T cells

(See article on pages 967–976.)

Only a subset of peptides from a given protein are immunoreactive, in part because MHC proteins and T-cell receptors (TCRs) are limited in their interactions with processed peptides. Glatiramer acetate (GA; also called copolymer-1) is a heterogeneous copolymer of four amino acids that are characteristically found in immunoreactive peptides. Although its mode of action remains controversial, GA has been known for almost 30 years to suppress immune responses to the human autoantigen myelin basic protein (MBP).

Originally devised to mimic MBP and to induce an immune response analogous to that seen in multiple sclerosis (MS), GA is now being used to suppress MS. GA interacts readily with class II MHC molecules on APCs and is believed to exert its beneficial effects by stimulating T cells promiscuously but weakly. In animal models, GA prevents the onset of experimentally induced immunity to MBP, and ongoing human trials show that long-term treatment with GA slows the progression of MS. Duda et al. have shed light on the effects of GA by studying T cell lines generated from MS patients before and during a long course of GA injections.

The authors measured the capacity of these T cells to proliferate in response to various antigens and also studied the cytokines that these treatments elicited. Antigens studied included well-defined autoepitopes associated with MS or other autoimmune diseases, as well as GA itself, and combinatorial peptide libraries, which represent still more heterogeneous mixtures of potentially antigenic epitopes. The extent of T-cell proliferation elicited by such a library serves as a measure of the degeneracy of the T-cell response, or how avidly a presented peptide must bind to TCRs to provoke a biological response. T cells shift, with treatment, toward a more characteristic Th2 cell response to GA and looser constraints on the structure of antigenic epitopes, but Duda et al find that the in vitro response of T cells to MBP peptide is quantitatively and qualitatively unchanged. The authors propose that GA inhibits MS through a bystander suppression mechanism, whereby GA-specific Th2 cells, which would be expected to promote immunological tolerance, proliferate and block disease progression despite the continued presence of MBP-specific T cells.