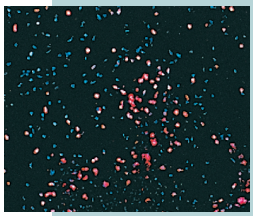
In this issue

By John Ashkenas, Science Editor

Complex effects of VLA-4 antibody on autoimmune disease

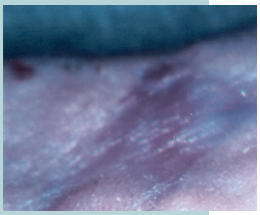
(See article on pages 995–1006.)



The course of multiple sclerosis (MS) often involves not a steady progressive decline of motor control, but a sequence of declines, punctuated by intervals of partial recovery. Work in a mouse model that mimics this "relapsing remitting" form of MS shows that the T cells involved at the onset of autoimmune disease differ from those that drive the later relapses. Thus, the epitopes recognized on the proteolipid protein (PLP) immunogen, which is used to initiate disease in this model, are different for the T cells that initially breach the blood-brain barrier and for the subsequent rounds of T-cell expansion seen later in the disease. Theien and colleagues have now identified another difference between these T-cell populations, related to their adhesive interactions. The integrin VLA-4 is implicated in adhesion of T cells to the endothelium, and several reports suggest that blocking antibody can ameliorate MS or other autoimmune disorders. Theien et al. find, however, that this treatment is only beneficial if begun early, before the onset of clinical disease. If applied later, this same antibody increases both the severity of disease and the rate of remission. The authors argue that T cells in an animal already primed to respond to PLP can reach their target in the CNS by interactions independent of VLA-4, and they suggest that the antibody exacerbates the response of these cells by mimicking the effect of normal costimulatory signals.

Vitamin D receptor deficiency sends fur flying

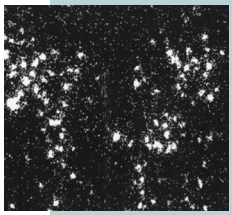
(See article on pages 961–966.)



Hair follicles consist largely of one epithelial cell type, the keratinocyte, and one mesenchymal cell type, the dermal papillar cell. Interactions between these two classes of cell are crucial for maintenance of the follicle and continued growth of hair. Sakai and coworkers have previously observed that mice lacking the vitamin D receptor (VDR), a nuclear receptor expressed in both of these cell populations, lose their hair early in postnatal life. Here, they test several models to explain this finding. Noting that the absence of feedback regulation ordinarily causes vitamin D levels to surge to potentially toxic levels in VDR-deficient animals, Sakai et al. used a controlled diet and a UV-free environment to generate mice of both $VDR^{+/+}$ and $VDR^{-/-}$ genotypes that completely lack this vitamin. Under these conditions, adult $VDR^{-/-}$ mice are still hairless, and $VDR^{+/+}$ mice still have normal coats, arguing that the absence of the receptor, rather than the presence of toxic quantities of vitamin D or the absence of the vitamin D–dependent signals, must account for the failure of the follicle to maintain hair growth into adult life. To determine whether this unexpected VDR function occurs in keratinocytes or papillar cells, the authors then used the $VDR^{+/+}$ and $VDR^{-/-}$ mice as a source of purified mesenchymal and epithelial cells and transplanted these cells into recipient mouse skin. Only the keratinocyte population, they show, requires VDR to sustain the normal hair cycle. How the VDR might support keratinocyte and follicle function even in the absence of its known ligands remains unclear.

Targeting thyroid hormone receptor isoforms

(See article on pages 1017–1023.)



Specialized neurons in the paraventricular nucleus of the hypothalamus produce thyrotropin-releasing hormone (TRH), a key regulator of thyroid hormone levels, and hence of metabolic rate. In a previous *JCI* paper, Abel and colleagues developed a mouse specifically lacking one of the alternatively spliced isoforms of the thyroid hormone receptor TR-β2, and they showed that TR-β1 and the other receptor isoforms are expressed normally in these mutant animals. TR-β2 is restricted in its expression but is found prominently in TRH neurons. Following up on hints that the different isoforms carry out distinct functions in thyroid hormone regulation, these same authors now show that TR-β2 is required for the silencing of TRH expression. TRH is therefore highly expressed in the mutant mice under basal conditions, but it does not respond to either hypothyroid conditions or treatment with exogenous thyroid hormones. As predicted, the animals are capable of regulating TRH in response to leptin and other stimuli, confirming that the defect is specific to the feedback system that regulates thyroid hormones.