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By John Ashkenas, Science Editor

Intrakine blockade of a chemokine receptor

(See article on pages 269–277.)

In one clever but still unproved scheme for blocking the progression of AIDS, a so-called "intrakine" is to be transduced into lymphocytes to prevent surface expression of a molecule required for HIV entry. Infection by HIV depends in part on the surface protein CXCR4, a receptor whose endogenous ligand is the chemokine SDF-1. Earlier work showed that an engineered SDF-1 variant that is retained in the endoplasmic reticulum has a dominant effect on CXCR4, preventing the receptor from reaching the cell surface and thus rendering the cell resistant to HIV. Clinical tests of this approach are ongoing, but meanwhile Zeelenberg and colleagues have used the same system to examine other cellular effects of loss of CXCR4 surface expression. They show here that T lymphocyte–derived hybridomas — usually an invasive cell type that can cross multiple barriers to reach target organs — lose their ability to migrate in response to SDF-1. These transfected hybridomas fail to cross cell monolayers in culture or to exit the bloodstream when introduced in vivo. A control intrakine that blocks surface expression of a different chemokine receptor, CCR4, does not affect the ability of these cells to disseminate or generate malignant tumors, indicating that SDF-1 signaling is specifically required for invasive behavior by these cells. Whether normal T cells also depend on the SDF-1/CXCR4 interaction to reach their target tissues is not clear, but if so, the SDF-1 intrakine strategy for treating AIDS may prove to be immunosuppressive in its own right.

Lymphocytes in early atherogenesis

(See article on pages 251–259.)

In addition to their characteristic accumulation of macrophage-derived foam cells and proliferation of smooth muscle cells, atherosclerotic lesions contain T lymphocytes, predominantly of the Th1 class. Despite some evidence that these cells respond to epitopes that are found in the lesion, their role, if any, in the disease process has been hard to pin down. Song et al. have now revisited this question by following lesion progression in the atherosclerosis-prone *LDLR*$^{-/-}$ mouse strain, comparing *LDLR*$^{-/-}$ animals, which have a full complement of lymphocytes, with littermates of the double knockout genotype *LDLR*$^{-/-}$ *RAG1*$^{-/-}$, which are devoid of B and T lymphocytes. The presence or absence of lymphocytes does not affect the ultimate outcome of feeding these mice a cholesterol-rich diet, but the authors find that the early events of lesion growth are slowed in double knockout mice. These findings are at odds with some earlier studies that examined the role of lymphocytes in pathogenesis in the apoE-deficient strain, another widely studied atherosclerosis-prone model. Song et al. argue that their system more accurately matches human pathogenesis, in part because apoE deficiency (but not LDLR deficiency) leads to impaired innate immune responses, a change that is not seen in humans with heart disease. Since *RAG1*$^{-/-}$ mice lack all lymphocytes, it will be important to examine the specific contributions of Th1 cells and other lymphocyte subtypes to this disease process.

Hammering out the role of IDX-1 in diabetes

(See article on pages 319–329.)

The Habener lab, which has previously implicated the transcription factor IDX-1 in pancreatic development and function, has now engineered a mouse strain in which to study the influence of this protein on diabetes. The importance of IDX-1 extends well beyond its ability to regulate insulin transcription, as seen in IDX-1–deficient mice, which lack a pancreas entirely. Since weak expression of IDX-1 leads to adult-onset type 2 diabetes in both mice and humans, it has been proposed that diminished IDX-1 function, even in the absence of *Idx1* mutations, could contribute to pathogenesis. Indeed, IDX-1 expression is reduced in hyperglycemic animals, but it has not been clear whether this change is a cause or a consequence of the progression of diabetes. To test this matter directly, Thomas et al. placed a hammerhead ribozyme specific for the IDX-1 mRNA under control of an inducible promoter. They show that the ribozyme can destabilize the IDX-1 mRNA and suppress glucose-dependent activation of the *Insulin* promoter. Interestingly, the effects of this ribozyme are limited because of a previously unsuspected autoregulatory loop through which loss of IDX-1 protein stimulates IDX-1 transcription. Nevertheless, when the ribozyme transgene is activated chronically, male mice show signs of glucose toxicity. Because the symptoms only become apparent in older males, Thomas et al. suggest that the IDX-1 autoregulation is impaired during aging, an event that may compromise the ability of the pancreas to maintain adequate insulin expression.