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In This Issue

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Metalloproteinases choreograph disc resorption (See articles on pages 133–141 and 143–150.) Matrix metalloproteinases (MMPs) degrade a wide variety of extracellular matrix (ECM) proteins, and so it comes as little surprise that enzymes of this class could promote the breakdown of intervertebral disc proteoglycans during the resorption of herniated discs. However, Haro and colleagues have now established an organ culture model of this healing process, and they show in this pair of papers that MMPs act, not simply to catabolize ECM in the disc, but rather to regulate complex cellular interactions that ultimately promote herniated disc resorption. In their system, discs co-cultured with activated macrophages break down, losing roughly half of their wet weight within 3 days, but the absence of MMP expression in macrophages or disc chondrocytes can cause this process to go awry. The authors show that efficient expression of MMP-3 and -7 requires chondrocytes and macrophages to be cultured together, and they observe the induction of the MMPs in each cell type during co-cultivation. Expression of MMP-7 by macrophages stimulates chondrocytes to express MMP-3, and this induction appears to be critical for disc ECM breakdown, since macrophages that lack MMP-7 fail to stimulate chondrocytes and do not invade the disc. Haro et al. demonstrate that MMP-7's effects are mediated by the release of soluble tumor necrosis factor (TNF-α) […]

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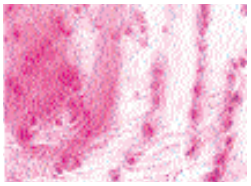

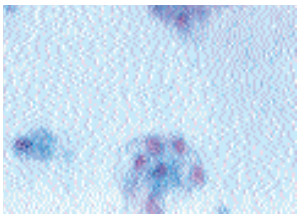

Leptin-dependent HDL uptake

(*See article on pages 151–159.*)

Cholesterol esters transit into cells from HDL particles through a process that is distinct from the familiar endocytotic pathway worked out for LDL. This novel pathway involves tethering of the HDL particle to scavenger receptor type B-I (SR-BI) molecules on the cell surface, but these receptors do not ferry the HDL apoproteins (or the residual HDL lipid) into the cell. Nevertheless, the HDL apoproteins enter cells, where they may be degraded or rereleased into the extracellular space. Here, Silver et al. report that this ill-defined endocytotic pathway is regulated by leptin, the product of the *ob* gene. Noting that *ob/ob* mice accumulate high levels of HDL apoproteins in their plasma, these authors followed the uptake of labeled HDL into primary hepatocytes from wild-type or mutant mice. Wild-type cells, the authors find, internalize HDL apoproteins efficiently, routing them through a perinuclear endosomal recycling compartment before secreting them back into the medium, and in these cells only a small proportion of the endocytosed material is degraded in lysosomes. *ob/ob* hepatocytes, on the other hand, are defective in HDL recycling, although they carry normal levels of SR-BI. These mutant cells take up HDL apoproteins inefficiently and sort most of them to the lysosome. In addition to sorting the endocytosed protein anomalously, *ob/ob* cells contain relatively little cholesterol in their perinuclear membranes. However, pretreatment of *ob/ob* mice with leptin restores both the uptake of apoproteins and the normal distribution of cholesterol within their hepatocytes, suggesting that a leptin-dependent HDL uptake pathway provides much of the cholesterol in these membranes. The endocytosing receptor for HDL apoproteins remains unknown, but the finding that the pathway responds to leptin may prove useful for characterizing known apoprotein-binding proteins and for identifying novel candidate receptor proteins.