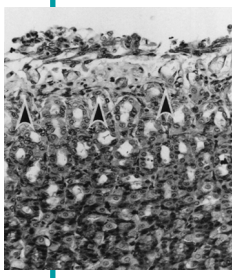
In this issue

By John Ashkenas, Science Editor

Statins' beneficial effects on HDL

(See article on pages 1423–1432.)

Statins are a widely prescribed family of drugs that lower levels of LDL by blocking synthesis of the cholesterol precursor mevalonate. In addition, these drugs have several other effects that are also potentially antiatherogenic, notably an increase in levels of HDL and its associated apolipoprotein A-I (apoA-I).



Martin et al. have investigated the basis of this induction, which they show occurs as a consequence of *apoA-I* promoter activation in cells depleted of mevalonate. In the course of this work they have uncovered an unsuspected link between the transcription factor PPARα, which activates apoA-I expression, and the transcriptional response to statins. As the authors note, mevalonate is not only required as a precursor to cholesterol and related sterols but is also essential to maintain levels of nonsterol lipids, which have important structural and regulatory functions. In particular, they are required for the lipid modification (geranylgeranylation) of the Rho family of protein kinases. Martin et al. define the outlines of a pathway whereby geranylgeranylated RhoA suppresses PPARα activity. By blocking mevalonate synthesis, statins apparently derepress PPARα and thereby activate apoA-I transcription and the biosynthesis of HDL. This work defines a second branch of the pathway by which statins regulate the profile of lipoproteins in the blood. The first, now-classical branch involves sterol lipids and blocks LDL synthesis. The second involves the nonsterol products of mevalonate and PPARα and induces HDL synthesis. Filling in the details of the second branch may identify novel players that could be targeted specifically to increase reverse transport of cholesterol for therapeutic benefit.

PAR-2 and gastric secretion

(See article on pages 1443–1450.)

Kawabata and colleagues have shown previously that the protease-activated receptor PAR-2, which is expressed in sensory neurons throughout the gastrointestinal tract and elsewhere, activates secretion by the salivary gland and the exocrine pancreas. This receptor, which may be best known for its ability to induce smooth muscle relaxation in the vasculature and bronchioles, is unusual in that it carries its own ligand as part of its sequence. As the name suggests, proteolytic cleavage of the receptor frees the ligand to bind and activate the receptor, so PAR-2 signaling normally depends on the presence of trypsin or other proteinases, but it can be stimulated artificially by providing the activating sequence in a synthetic peptide. Here, Kawabata et al. show that such peptides can stimulate sensory nerves in the stomach and activate the secretion of gastric mucus. As expected, given the presumed protective role of this mucus, PAR-2 agonists block erosion of the stomach lining in rats with high levels of gastric acid. This finding may point the way to useful preventative treatments for gastric ulcers, including those that result from heightened acid secretion caused by chronic use of aspirin or other common analgesics.

Chemokines in allergic asthma

(See article on pages 1357–1364.)

The recognition of two major classes of helper T cells, Th1 and Th2, has focused attention on the distinctive sets of cytokines produced by these cells and on their role in activating or suppressing inflammatory responses. More recently, it has become clear that Th1 and Th2 cells also differ with respect to the chemokine receptors they express, a finding that may help explain the different timing of their entry into inflamed tissues. Now, Panina-Bordignon and coworkers have studied the expression of chemokines and chemokine receptors in the inflamed airways of asthmatic subjects. They find that two Th2-restricted chemokine receptors, CCR4 and CCR8, are upregulated in the asthmatic lung following challenge with inhaled allergens. Several chemokines that bind CCR4 are also induced under these circumstances, suggesting a mechanism by which Th2 cells are activated to infiltrate the mucosa of the lung. Although the known CCR8-specific chemokines are not induced, the authors find that the number of CCR8-positive cells correlates with the severity of the asthmatic response, so this receptor may well be important in this disease pathway. The induction of CCR4 and its ligands appears to be specific for atopic disease, since a similar pattern is seen in atopic dermatitis but not in chronic obstructive pulmonary disease, which is thought to be driven by Th1 responses.