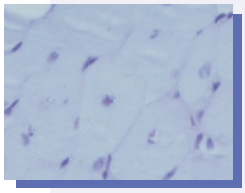
In this issue

By John Ashkenas, Science Editor

Lipoprotein lipase: location, location, location

(See article on pages 1183–1192.)

Many extracellular proteins bind avidly to heparin in vitro, reflecting their affinity, in a physiological setting, for the long polysaccharide side chains of heparan sulfate proteoglycans (HSPGs). In most cases, the significance of this interaction in vivo is not clear. Lutz and colleagues previously identified a putative heparin-binding site in the secreted enzyme lipoprotein lipase (LpL), and they have now generated a transgenic mouse line expressing a version of human LpL that is mutated at this short sequence. The mutant protein binds poorly to heparin and loses activity rapidly when expressed either in cultured cells or in mice. Native LpL is active as a homodimer, but the mutant form readily dissociates into inactive monomers, suggesting that HSPGs help maintain the quaternary structure of the protein. The mutant LpL also fails to localize properly: Wild-type LpL remains firmly attached to the lumen of capillaries and releases lipoprotein-derived lipids at this site, whereas the mutant protein is only transiently associated with the capillary bed and is rapidly shed into the bloodstream. Not all of the released protein is inactive, so lipoprotein metabolism begins in the bloodstream of transgenic mice. The generation of fatty acids within the circulation, rather than in the muscle and other tissues, profoundly alters the blood lipid profile of LpL transgenic mice, even those that also carry the normal gene and express the native enzyme at its usual location.



Gene therapy for diabetic neuropathy

(See article on pages 1083–1092.)

Blisters to the feet, a mere annoyance for most people, are a grim and sometimes life-threatening danger for diabetics, whose ulcerations can be so serious that they require amputation of the lower leg. These injuries occur because of nerve degeneration, which reduces pain perception the lower leg. Although the biochemical link between hyperglycemia and this peripheral neuropathy remains a matter of debate, the same symptom occurs in patients with type 1 and type 2 diabetes and can be observed in animal models of both conditions. Isner and his colleagues recently showed that a similar neuropathy, this one arising from ischemia in the hindlimbs, results from loss of blood flow within the vessels that support the nerves, and they found that this response can be blocked using VEGF therapy to increase the growth of these vessels. Here, the same group shows that diabetic neuropathy causes a dramatic loss of vessels in the sciatic nerve in rat and rabbit models of diabetes. Systemic injection of naked DNA encoding VEGF restores vascular function and blood flow within this nerve and can maintain or even restore nerve function. Based on some tests of VEGF gene therapy on humans, including some diabetics, the authors suggest that this treatment may not lead to complications that result from uncontrolled vascular growth in other tissues.

Trapping metalloproteinases in a serpin's coils

(See article on pages 1117–1126.)

Serpins are a family of proteinase inhibitors that bind to the catalytic sites of serine-dependent proteinases. Tissue factor pathway inhibitor-1 (TFPI-1), a well studied member of this family, is best known for its ability to limit the clotting cascade. Based on its structural similarity to TFPI-1, the related protein TFPI-2 was expected to play a similar role, and indeed, TFPI-2 can bind various serine proteinases. Nevertheless, TFPI-2 has proved to be a poor inhibitor of these enzymes, so its physiological role has been uncertain. Herman et al. show here that TFPI-2 acts instead on a distinct class of targets, the matrix metalloproteinases (MMPs), which are required to degrade collagen and other ECM components that are typically not the targets of serine proteinases. This biochemical activity is independent of TFPI-2's action as a serpin, since it can block MMP activity even when it has been preincubated with serine proteinases. TFPI-2 is secreted by vascular smooth muscle cells and is abundant in healthy arteries, where it would be expected to protect the vessel intima from degradation by MMPs. The authors focus on atheromatous plaque, a collagen-rich structure that can rupture to cause strokes. Within this plaque, TFPI-2 is enriched in the fibrous cap but is more sparse in the adjoining "shoulder" region, where collagenase-secreting macrophages reside. Because this region of the atheroma is known to be a frequent point of rupture, the authors speculate that it is destabilized by a local imbalance between TFPI-2 and MMPs.