In this issue

By John Ashkenas, Science Editor

Decorin as a conduit for Lyme disease bacteria

(*See article on pages 845–852.*)

As Lyme disease progresses past the early stage of a rash in the region of the initial infection, spirochetes circulate throughout the body and infect various organs. Lyme arthritis occurs when the pathogens colonize the joints, and Brown and colleagues have now identified a molecular interaction between host and pathogen that seems to be particularly important for this aspect of the disease. *Borrelia burgdorferi* spirochetes interact with host ECM components through multiple adhesive receptors, including two surface proteins that bind specifically to decorin, a proteoglycan associated with interstitial collagen in the skin and cartilage. Decorin-deficient mice show only relatively subtle phenotypes in most respects, and when they are infected with *Borrelia*, either by direct injection or by being bitten by infected ticks, the spirochetes become disseminated to most tissues at nearly normal levels. Nevertheless, the absence of decorin confers on these animals a significant protection from Lyme arthritis, especially at low doses of bacteria. These mutant mice are similar to wild-type animals in their immune responses to *Borrelia* and in their sensitivity to other forms of pathogen-induced arthritis, suggesting that adhesion to decorin is specifically involved in disseminating the spirochete to the joints of infected animals.

How fat kills heart cells

(*See article on pages 813–822.*)

Droplets of stored lipids accumulate in the cytoplasm of cardiac myocytes in a variety of cardiomyopathies, ranging from such chronic conditions as diabetes and obesity to the pathology that leads to sudden death in otherwise healthy young people. Still, it has been difficult to judge whether excess lipid storage reflects some other underlying pathology or whether it contributes directly to the death of heart muscle. Chiu and coworkers have tested this matter by forcing the overproduction of long-chain fatty acyl CoA in cardiac myocytes, using an enzyme that helps retain fatty acids in the cell following uptake. As a consequence of overexpressing the acyl-CoA synthetase (ACS1), long-chain fatty acids accumulate more rapidly than the cell can consume them or dispose of them, and they are stored in the form of triglycerides and other lipids. Chiu et al. show that ACS1 transgenic lines die prematurely, at a rate proportional to the level of enzyme overexpression. In these animals, cardiac myocytes die through apoptosis and necrosis, and those cells with with large lipid inclusions are lost preferentially. Interestingly, ceramide, a lipid mediator of apoptosis, is one of the species that accumulates in the hearts of these animals. While inhibition of ceramide signaling might therefore be protective, the authors note other quantitative and qualitative features of cellular lipids — differences that could also contribute to the pathology seen in this model and, presumably, in humans with certain forms of cardiomyopathy.

Collagen and osteoporosis

(*See article on pages 899–907.*)

Common conditions such as osteoporosis often show clear evidence for a genetic component, but pinning the risk of disease on a specific genetic polymorphism is notoriously tricky in these cases: Biologically plausible candidates abound, and evidence implicating a particular mutation in the disease process can be difficult to reproduce. In the case of osteoporosis, one candidate that has been tested repeatedly is a single nucleotide polymorphism in the collagen gene *COL1A1* in a sequence that interacts with the transcription factor Sp1. Now, Mann et al. have revisited the vexed question of whether this polymorphism is indeed associated with fragile bones and frequent fractures. First, they performed meta-analysis on 15 studies reported over the last 5 years, dealing with the effects of the Sp1 site polymorphism. In aggregate, they find that carrying one of the two alleles, termed "s", in homozygous form correlates with a loss of bone mass density. The ss genotype predicts a nearly twofold greater risk of vertebral fractures relative to SS homozygotes, with Ss heterozygotes experiencing intermediate effects. Turning to the molecular effects of this polymorphism, they show that, at least in cultured human osteoblasts, the s allele generates higher steady state levels of COL1A1 mRNA than does the S allele, perhaps as a result of more efficient Sp1-dependent transcription. This difference in transcript level further correlates with an increase in the relative amount of the α1(I) collagen chain, the product of this mRNA, in the mature collagen produced by cultured osteoblasts. The authors argue that differences in collagen trimer subunit composition may explain the mechanical and biochemical features they see in the bones of individuals carrying the s allele.