MEDICAL GENETICS

Arterial hardening in mice

James Scott

BY giving mice a gene that nature failed to, or, perhaps by a quirk of evolution, carelessly lost, R. M. Lawn and colleagues have managed to develop an animal model for atherosclerosis. The gene, for the blood protein apolipoprotein (*a*), is apparently missing from rodents and most other non-primate species (apart from the European hedgehog). When expressed in mice, as Lawn *et al.* describe on page 670 of this issue[1], the gene leads to the development of atherosclerosis in those mice on high-fat diets.

Atherosclerosis is a multifactorial disease of arterial hardening and fat deposition with both genetic and environmental components. The main risk factors are hypertension, dyslipoproteinaemia, coagulation disorders and cigarette smoking. However, with one exception (homozygous familial hypercholesterolaemia), there is no direct relationship between a single aetiological component and the development of the disease. Direct proof that an abnormality identified in population-based studies causes disease has been elusive, but is now rapidly becoming available as genes encoding key components for lipid transport in blood are either overexpressed in transgenic mice or knocked-out by homologous recombination[2].

Besides Lawn and colleagues' transgenic study, reports have appeared in recent issues of *Cell*[3] and *Science*[4] showing that knocking out expression of apolipoprotein E produces massive hypercholesterolaemia and profound atheroma even on a normal diet. And it seems that overexpression of apolipoprotein A-I[5] and of the low-density lipoprotein receptor[6] and its ligand apolipoprotein E[7] (reported by E. Rubin at a recent meeting in Shizuoka, Japan) can protect susceptible mouse strains against diet-induced atherosclerosis.

In human population studies, lipoprotein (*a*) levels higher than 0.3 mg ml^{-1}, have been found in one in five individuals and are associated with a susceptibility to atherosclerosis, and therefore to myocardial infarction and stroke[8]. Lipoprotein (*a*) (Lp(*a*)) consists of a low-density lipoprotein (LDL)-like particle with a second protein; apolipoprotein (*a*) (apo(*a*)) tightly associated with the apolipoprotein apoB-100. Apo(*a*) is closely related to plasminogen, from which the enzyme that hydrolyses fibrin blood clots is released by tissue-plasminogen activator. The apo(*a*) molecule is composed of a variable repeat of plasminogen at its amino terminus, a disulphide-bonded kringle domain shaped like a Danish pastry, known as kringle IV, a single kringle V, and the plasminogen protease domain. Apo(*a*) may be bonded to apoB-100 by a disulphide link, an association presumed to come about in the endoplasmic reticulum (ER), but we know from studies of patients with abetalipoproteinaemia — a rare mendelian recessive disorder in which apoB-100 is synthesized but not secreted — that apo(*a*) can be secreted in the free form[9].

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Deposition pattern of apo(*a*) in an atherosclerotic lesion of a human coronary artery. Immunohistochemical staining of the fibroatheroma demonstrates the accumulation of the apoprotein in bundle-like (open arrows) and punctuated (solid arrows) patterns, with the extracellular matrix. Staining for apoB-100 in a serial section shows almost identical patterns, revealing that the two are bound as Lp(*a*). (Micrograph courtesy of A. Niendorf and U. Beisiegel.)

In mice transgenic for human apo(*a*), this apolipoprotein is 95% free in the circulation[10] (the baboon, too, secretes much of its apo(*a*) in the free form[11]). When human LDL particles are infused into these transgenic mice they rapidly become tightly associated with apo(*a*) to form Lp(*a*) and can be dissociated only by reducing agents[10]. Although these experiments demonstrate the high affinity of apo(*a*) for apoB-100, they do not prove that a disulphide bond is formed, but human apo(*a*) probably cannot associate with murine apoB-100 because of the lack of conservation of cysteine residues at the carboxy terminus of rodent apoB-100[12,13]. Normally, once apoB-100 (always in excess) and apo(*a*)

RESUMÉ

SPOT the difference

PARTICIPANTS at last week's meeting of the American Geophysical Union, in San Francisco, were treated to the first ever satellite video of fault motion. R. L. Crippen of the Jet Propulsion Lab prepared the video from just a pair of pictures of the Mojave Desert in California where the Landers earthquake occurred earlier this year, one archival and one specifically requested after the rupture. Although the fault movement was less than a pixel, by flickering between the two frames, obtained with the French remote-sensing satellite SPOT, Crippen could discern the changed shadowing of the land form and even new fractures. The Global Positioning Satellite (GPS) system gives better spatial resolution, but it relies on sensors already put in place; Crippen's approach required no preparation.

Not so deadly

GENETIC engineering has given plants of deadly nightshade (*Atropa belladonna*) in which the alkaloid hyoscyamine, which this plant makes in abundance, is converted almost completely into the more commercially valuable alkaloid scopolamine, an anti-cholinergic drug used, for example, to prevent travel sickness. By inserting extra genes for the hydroxylase that converts hyoscyamine into scopolamine, and ensuring that they are expressed constitutively, D.-J. Yun *et al.* (*Proc. natn. Acad. Sci. U.S.A.* **89**, 11799–11802; 1992) produced plants containing most of the alkaloid content of leaves and stems as scopolamine. This also makes extracting the drug much easier; it can be simply crystallized out instead of being separated by chromatography from a complex mixture of alkaloids.

Flash of inspiration

OBSERVATIONS of γ-ray bursts by the Compton Gamma Ray Observatory have re-ignited a controversy: do the bursts come from our own Galaxy, or are they at cosmological distances? In principle, there is an easy test: if M31, the nearby Andromeda galaxy which closely resembles ours, has the same population of γ-ray bursts as our own Galaxy, then a sufficiently sensitive detector could spot them. Unfortunately, the Compton detector is not sensitive enough. But in the *Astrophysical Journal* (**400**, L59–L63; 1992) H. Li and E. P. Liang remark that X-ray flashes are sometimes associated with γ-ray bursts, with a typical relative output of a per cent or so. ROSAT, the X-ray satellite, is sensitive enough to see X-rays from M31, if all γ-ray bursts produce X-ray flashes at the 2 per cent level (which may not be the case). Several weeks' observation of M31 could then decide whether the bursts are galactic or not.