adds that interferons have found niches in oncology for the treatment of certain leukaemias and lymphomas[8], and 'there may well be novel or existing inflammatory cytokines that could be used in combination therapies,' he says. Although Thomas-Tikhonenko admits that the search for an anti-angiogenic agent that will be useful in humans is still at the 'blue-skies' stage, he remains optimistic: 'A factor that can inhibit angiogenesis is something of a 'Holy Grail' – many are looking for it, perhaps we will be lucky.'

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Unravelling metabolic syndrome X

Sharon Dorrell, Freelance writer

A recent Canadian study reports an association between a rare autosomal dominant form of insulin resistance – Dunnigan-type familial partial lipodystrophy (FPLD) – and early coronary heart disease (CHD)[1]. According to Robert Hegele (Robarts Research Institute, London, Ontario, Canada), who carried out the study, this link is significant because the mutation of the *LMNA* gene that underlies FPLD and causes defects in the nuclear envelope also gives rise to a phenotype that resembles the insulin resistance syndrome (metabolic syndrome X; Box 1). A better understanding of FPLD could shed light on the mechanisms underlying insulin resistance in the general population, and perhaps eventually lead to improved treatments.

LMNA mutations

LMNA encodes for lamin A and C, which are components of the nuclear lamina, the mesh-like structure on the inner surface of the nuclear envelope. Two rare missense mutations in *LMNA* (R482Q and R482W) were discovered in Canadian FPLD families. Hegele's study found a higher prevalence of CHD among 23 heterozygous *LMNA* missense mutation carriers, all of whom were insulin resistant. Eight patients had CHD compared with only one of 17 homozygous family control subjects. Moreover, six of the patients with CHD had experienced heart attacks, coronary artery bypass grafts, or other CHD endpoints by the age of 55. The women in the group appeared to be particularly susceptible to these early CHD events.

'The *LMNA* mutations probably do not directly cause atherosclerosis,' says Hegele. 'Instead, the mutations appear to affect fat cells only, but in a very specific way that gives rise to the characteristic presentation of FPLD.' FPLD first becomes evident at the onset of puberty when those affected begin to lose fat from their extremities and the gluteal region until no fat is stored at these sites. Their central fat stores in the abdomen, face, neck, and shoulders are, however, unaffected and become the only place fat can be stored. Consequently, says Hegele, 'when people with this condition gain weight, the only place for the fat to accumulate is centrally and, as adults, these people exhibit an extreme form of central obesity.'

Hegele adds that he cannot yet explain why women with FPLD appear to be more susceptible to CHD events than men. It has been known for a while that diabetes eliminates the protection from atherosclerosis enjoyed by premenopausal

Box 1. Insulin resistance and metabolic syndrome X

In insulin-resistant individuals, insulin fails to stimulate glucose uptake and hyperinsulinaemia ensues to maintain glucose balance. Hyperinsulinaemia is associated with a cluster of metabolic complications that increase the risk of coronary heart disease, including glucose intolerance, dyslipidaemia and hypertension. Together, these complications are known as the insulin resistance syndrome or metabolic syndrome X, a syndrome that often occurs in people with central obesity.

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women but, he says, 'the presence of diabetes would, therefore, be expected simply to equalize the appearance of these endpoints between men and women. The excess CHD seen in female FPLD subjects is, therefore, interesting, but unexplained.'

Insulin resistance and the general population

As expected, the insulin-resistant FPLD patients had an increased incidence of type 2 diabetes, hypertension and dyslipidaemia than their unaffected relatives. They also had elevated triglyceride levels and depressed high-density lipoprotein (HDL) cholesterol levels. They did not, however, have raised low-density lipoprotein (LDL) cholesterol levels. 'An important point of this study', says Hegele, 'is that people can develop atherosclerosis even when their LDL level is relatively normal. This is an important concept, because the role of high LDL levels as a lipid risk factor for atherosclerosis is accepted as doctrine.'

Central obesity in the general population is known to be associated with insulin resistance, abnormal lipid profiles (high triglycerides and low HDL), hypertension and atherosclerosis. Similarly, in people with FPLD, the genetic form of central obesity is associated with them same complications. They are, however, much more pronounced and occur at a younger age than in the general population. 'It is likely that it is the cumulative burden of these risk factors that predisposes FPLD sufferers to early atherosclerosis,' says Hegele.

New therapies

Although the complications of FPLD, such as hypertension, dyslipidaemia and type 2 diabetes, are treated with standard therapies, there is not yet any specific treatment for FPLD. Treatments such as parenteral leptin and the antidiabetic agents, the thiazoladenediones, are under investigation as possible ways to prevent fat loss or recover lost fat cells. However, it is unlikely that specific treatments will emerge until the precise role of the *LMNA* gene product, the lamins, is elucidated. Indeed, studies suggest that they could be more than simple nuclear envelope proteins[2]. If, however, a treatment can be found, says Hegele, 'then it could have implications for regular insulin resistance.' He concludes that, 'new insights from research in this area could also help understand the acquired lipodystrophy that affects people with HIV and who are treated with protease inhibitors.'

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