The pig: a new model of diabetic atherosclerosis

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A new swine model of accelerated diabetic atherosclerosis has been developed that could, for the first time, provide an accurate model for this condition. The model, developed by a team from the Medical College of Georgia (Augusta, GA, USA), could enable researchers to test drugs that not only control the atherosclerotic process but that can also prevent restenosis after balloon angioplasty and stenting[1].

'Diabetics don't die of diabetes; they die of the complications from diabetes, and in particular they die of cardiovascular disease,' says Ross Gerrity, an experimental pathologist and Professor of Pathology from the Medical College of Georgia, who led the team. 'We really don't understand why this is.'

Patients with diabetes have a two–sixfold greater risk of developing atherosclerosis than non-diabetic individuals[2], and the most common cause of death in adult diabetic patients is coronary heart disease[3]. This excess risk occurs in both type 1 and type 2 diabetes[3]. In contrast to non-diabetic subjects, heart disease in diabetics occurs earlier in life, affects women almost as often as men, and is more frequently fatal[3].

A major factor that has limited the study of the mechanisms responsible for accelerating atherosclerosis in diabetics has been the lack of a suitable humanoid animal model.

Although genetic and induced rodent models have proved useful in studying other aspects of diabetes (such as retinopathy, kidney disease and glucose metabolism) they are poor models of diabetic atherosclerosis, because they develop non-humanoid lesions and have lipid and lipoprotein metabolism and profiles that differ markedly from humans.

Atherosclerosis in pigs

Researchers have noted that the atherosclerotic process in swine has much more in common with that in humans[4,5]. Pigs are omnivores, develop spontaneous atherosclerosis with increased age and have lipoprotein profiles and metabolisms similar to that of humans[6,7]. As in humans, coronary arteries in hyperlipemic swine typically develop major lesions in the first 2–3 cm of their origin. Furthermore, the rapid calcification of lesions – which is generally not prominent in animal models and is considered to be a particularly humanoid characteristic – is also observed in diabetic pigs[1].

Gerrity and colleagues, therefore, used the pig to develop a new model of diabetes by giving young, male, Yorkshire swine a cytotoxic compound, streptozotocin, which destroys the insulin-producing β-cells in the pancreas.

Streptozotocin was given for three days in a row, and then sections of the pancreas were taken from euthanized animals on day four, and weeks 1, 2 and 20, and stained with an antibody to insulin to visualize the β-cells. Counts of the number of β-cells per unit area of section showed a reduction in the number of β-cells to 6–12% of the normal value within days after the treatment[1].

'We find that if we can reduce the population of β-cells to <20% of the normal value, we can maintain the diabetic state. Even if glucose levels do return to normal we find that the animal has become glucose intolerant (equivalent to type 2 diabetes) and still gets accelerated vascular disease,' says Gerrity.

In further experiments, Gerrity has compared diabetic swine on high-fat (containing 1.5% cholesterol and 15% lard) or regular diets with non-diabetic swine on high-fat and normal diets for periods of up to 48 weeks. Histological and biochemical studies at weeks 4, 8, 16, 20, 24, 32 and 48 show that diabetic swine with high lipid or fat levels have twice the level of blood-vessel disease seen in non-diabetic, high-lipid swine with comparable lipid levels. Furthermore, lesions in the coronary and iliac arteries were much more severe and complicated in diabetic swine, and two–threefold more occlusive than those seen in their non-diabetic counterparts. 'The study clearly demonstrated that, under comparable conditions of hyperlipemia, diabetes vastly accelerated atherogenesis compared with that seen in non-diabetic swine,' says Gerrity.

Alan Fogelman, Castera Professor and Executive Chair of the Department of Medicine at the University of California, Los Angeles (UCLA; Los Angeles, CA, USA), believes this research is promising for diabetics: 'The pig model of diabetes developed by Ross Gerrity and his colleagues is a major advance in providing a model of diabetes of sufficient size and similarity to humans, to allow studies that will be of great importance to the treatment of human diabetics.'

Future studies

The team intend to use their model to examine cellular mechanisms responsible for the accelerated atherosclerosis in diabetes, and to test the effects of different anti-diabetic drugs on the atherosclerotic process.

Although the improvement of glycemic control might reduce the risk of heart disease in type 1 diabetic patients,

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insulin-treated type 2 diabetic patients continue to have increased risk of cardiovascular events[3]. 'We intend to examine the effects of glucose-lowering drugs such as insulin, as well as other anti-diabetic drugs, on accelerated atherosclerosis. Unlike insulin, these drugs do not control blood-glucose levels, and could include anti-inflammatory drugs, inhibitors of second-messenger systems and factors mediating smooth-muscle proliferation and monocyte and macrophage function,' says Gerrity

In collaborative studies with diabetologist Jerry Nadler and cardiologist Ian Sarembock from the University of Virginia Health Sciences Center (Charlottesville, VA, USA), Gerrity and colleagues are performing angioplasty and stent procedures in these diabetic swine. This follows from observations that diabetic people who have undergone these procedures are more likely to restenose than non-diabetic controls[8]. The size and structure of the swine heart and arteries are such that the same angioplasty catheters and stents used in humans can be used in pigs. Preliminary studies by the group have shown that stents in diabetic swine do restenose more rapidly than in those in non-diabetic swine. The ultimate objective of the study is to see whether effective glucose control with insulin, or other anti-diabetic drugs, can be used to prevent the process.

'Our model provides an excellent system in which to carry out mechanistic studies aimed at furthering our understanding of diabetic atherosclerosis, and to test the effects of existing and experimental pharmaceutical interventions on both disease progression and stent restenosis, both of which are major concerns for diabetics,' says Gerrity. Hopefully, interventions that are successful in this humanoid model could rapidly be transferred into clinical trials in humans.

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New method links multiple genes to complex diseases

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One of the greatest challenges facing human geneticists is to identify the genes influencing complex, multifactorial diseases. Researchers at Vanderbilt University (Nashville, TN, USA) have developed a statistical technique that allows multi-locus genetic effects to be identified from studies involving relatively small patient samples[1].

Most common diseases have no clear pattern of inheritance. However, many are strongly suspected to have a genetic component, which probably involves subtle interactions between polymorphisms in several different genes. The interaction of genes with environmental factors could also have a role.

Data reduction

Traditional parametric statistical techniques are of limited use in detecting which of many possible genetic combinations make a person susceptible to disease. Contingency tables generated from polymorphism data usually contain many empty cells, that is, genetic combinations that were not observed in the study. Large sample sizes are needed to make such studies statistically valid, and it is often prohibitively expensive to obtain genetic information from enough subjects.

Data reduction methods have been used successfully to analyze quantitative genetic traits[2]. Inspired by this, the Vanderbilt group has developed a computer-based method called multifactor-dimensionality reduction (MDR)[1]. Designed to analyze discrete traits in case-control and discordant sibling-pair studies, it can detect and describe gene–gene and gene–environment interactions involving as many as ten or more different gene loci.

MDR involves constructing a series of contingency tables showing the incidence of all the possible pairs of polymorphisms in cases and controls[1]. Each cell in the table is designated as either high or low risk depending on whether the combination of genotypes occurs more commonly in cases (high risk) or controls (low risk). This reduces the number of dimensions involved to one,

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