NEUROLOGICAL DISORDERS

A fusion of pathology in diabetic neuropathy

The fusion of proinsulin-expressing bone marrow cells with neurons could be a key event in the development of diabetic neuropathy, according to a recent report by Lawrence Chan and colleagues.

Diabetic peripheral neuropathy is the leading cause of non-traumatic limb amputations. The symptoms can be widespread, from numbness, pain and tingling of the extremities to problems with the digestive tract, bladder infections and impotence. But the chain of events that leads to nerve damage in diabetes is not well described, and current treatments are designed to relieve discomfort and prevent further tissue damage.

The main risk factor for diabetic neuropathy is hyperglycaemia, and the progression of neuropathy depends on the degree of glycaemic control in type 1 and type 2 diabetes. How hyperglycaemia leads to diabetic complications, including neuropathy, is unclear, but a number of factors have been implicated in the process.

Chan and colleagues had previously found proinsulin- and insulin-positive cells — which are normally confined to the pancreas — in various organs in mouse and rat models of diabetes, and had shown that most of these extrapancreatic insulin-producing cells originated in the bone marrow. In their latest study, the researchers discovered that in diabetic mice and rats with neuropathy, bone-marrow-derived cells that expressed proinsulin fused with neurons in the sciatic nerve and dorsal root ganglion, leading to cellular dysfunction and accelerated apoptosis.

The hybrid cells expressed proinsulin and tumour necrosis factor-α (TNFα), a cytokine that is known to be involved in peripheral neuropathy, and only neurons marked by proinsulin expression showed abnormal calcium homeostasis and apoptosis. Crucially, the researchers showed that the treatment of diabetic rats with insulin led to a reduction in the number of proinsulin-positive cells and prevented the prolongation of motor nerve conduction velocity — a sign of neuropathy — confirming that the appearance of these cells was due to hyperglycaemia.

How the mechanism described by Chan and colleagues relates to several other factors that have been implicated in diabetic neuropathy, including oxidative stress and growth factor deficiency, remains an open question.

Rebecca Craven

References and links

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NEURODEGENERATIVE DISORDERS

MEOX2 linked with Alzheimer's disease

Despite many recent advances, the pathogenesis of Alzheimer's disease is still unclear. Wu and colleagues bring us another step closer to understanding this process by describing how the gene *MEOX2* (mesenchyme homeobox 2, also known as *GAX*) contributes to neuronal and vascular dysfunction in this disorder.

Image courtesy of D. Jones.

The authors compared profiles of mRNA expression in diseased human brain endothelial cells with control samples to identify targets in Alzheimer's disease. This revealed that the expression of a small subset of genes, which includes the homeobox gene *MEOX2*, is altered in the disease — specifically, *MEOX2* is expressed at a lower level in cells affected by Alzheimer's disease than in healthy cells. Because homeobox genes have key roles in vascular differentiation, the authors speculated that restoring GAX expression could correct the abnormalities in the neurovasculature in Alzheimer's disease.

By first silencing and then restoring *MEOX2* expression, the authors showed that *MEOX2* plays an important part in two important processes. As well as stimulating the formation of new blood vessels (angiogenesis), a process that is impaired in Alzheimer's disease, restoration of GAX expression also increased the suppression of a transcription factor — the AFX-1 forkhead transcription factor — that is involved in apoptosis.

Following on from these findings, Wu and colleagues investigated the role of *MEOX2* in the clearance of the abnormal amyloid-β protein. Mice with only one copy of *Meox2* showed decreased expression of lipoprotein receptor-related protein 1 (LRP), which is a clearance receptor that is involved in the efflux of amyloid-β. However, the reduction in LRP expression was reversed on transduction of *Meox2* into diseased brain endothelial cells.

At present, there is no cure for Alzheimer's disease. The establishment of a link between the decreased expression of *MEOX2* and the impaired neurovascular functions that are thought to be involved in the pathology of this debilitating disease make this homeobox gene an attractive target for the treatment of Alzheimer's disease.

Samantha Barton

References and links

ORIGINAL RESEARCH PAPER Wu, Z. *et al.* Role of the *MEOX2* homeobox gene in neurovascular dysfunction in Alzheimer disease. *Nature Med.* 14 August 2005 (doi:10.1038/nm1287)