NEUROGENOMICS

A new look at lipids in nerves

Once myelination starts, Schwann cells have been regarded as rather quiescent cells that live in a 'maintenance state' in the adult. But the results of a functional genomic analysis published in *Genes and Development* challenge this view by identifying a subset of genes that are selectively upregulated in adult peripheral nerves. The products of some of these genes are linked to lipid metabolism, and their discovery in this context might have profound implications for the understanding of certain types of peripheral neuropathy.

Verheijen *et al.* performed a microarray analysis of mouse sciatic nerves at different stages of development (from embryos to adult) and myelination (from pre- to postmyelinating). They identified 685 genes that were differentially expressed in these samples; some of these genes had been previously linked to forms of peripheral neuropathy, validating this approach for the identification of new disease-related candidate genes.

The authors went on to cluster the differentially expressed genes on the basis of their temporal expression patterns, and identified a group of 286 genes that was selectively upregulated in adult, postmyelinating nerves. After further sorting of the genes on the basis of their biological function, Verheijen *et al.* found that some were related to the metabolism of lipids. Although many of them were expressed by the epineurium, which is populated by adipocytes, several genes were expressed in the endoneurium, which largely consists of Schwann cells and axons. This group of genes included the transcription factors *Srebp1* and *Srebp2*, which regulate the synthesis and uptake of cholesterol, and *Lpin1*, the product of which — the nuclear protein lipin-1 — is required for the proper development of adipose tissue. In fact, Verheijen *et al.* showed that mutations in *Lpin1* lead to peripheral neuropathy, and to the dysregulation of genes that participate in lipid metabolism in nerves.

As we do not know the nature of the relevant genes in about half of the known forms of inherited neuropathy, the data of Verheijen *et al.* provide us with a valuable lead for their identification. Furthermore, the finding that alterations in lipid metabolism are associated with nerve damage should help us to understand peripheral neuropathies that are seen in conjunction with metabolic disorders such as diabetes.

Juan Carlos López

References and links

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NEURODEGENERATIVE DISEASES

Controlling the BACEs

Amyloid-β peptide (Aβ), which aggregates to form the plaques that are a feature of Alzheimer's disease (AD) brains, is a product of the sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases. Data from two groups published in *The Journal of Cell Biology* identifies new control points in the APP processing pathway, manipulation of which could facilitate the development of treatments for this debilitating disease.

Several kinases that have been implicated in neurodegeneration catalyse the phosphorylation of threonine 668 (Thr668) of APP. As such, a team led by Li-Huei Tsai was prompted to investigate the role that this reaction might have in the development of AD. Their initial investigations revealed that phosphorylation of Thr668 was elevated in AD brains, particularly in the hippocampus. Subsequent immunolocalization studies showed that expression of Thr668-phosphorylated APP was coincident with that of hyperphosphorylated tau, tangles of which are another hallmark of AD brains.

Interestingly, Thr668-phosphorylated APP also colocalized with β-secretase (BACE1). This result hinted at a role for Thr668 phosphorylation in the regulation of BACE1 activity, a hypothesis that was lent credence when the production of Aβ was shown to be significantly reduced following inhibition of Thr668 phosphorylation. According to the authors, phosphorylation of Thr668 probably affects BACE1 activity indirectly by influencing the intracellular sorting and trafficking of APP and therefore its availability to the enzyme.

A more direct mechanism of regulation of BACE1 activity was demonstrated by Jeremy Turnbull and colleagues. This group wondered if heparan sulphate — proteoglycans of which are associated with Aβ plaques — might participate in Aβ production. *In vitro* assays showed that cleavage of APP by BACE1 was inhibited by heparan sulphate in a dose-dependent manner. Modification of the sulphation pattern of heparan sulphate and the number of saccharide monomers therein also influenced the degree of inhibition.

Affinity filter assays showed a direct interaction between heparan sulphate and BACE1. The authors suggest that, in the normal brain, endogenous heparan sulphate binds at or near the active site of BACE1, thereby preventing docking of its APP substrate, cleavage, and subsequent formation of Aβ fibrils. Perturbation of this interaction might contribute to the pathogenesis of AD, making it an attractive target for AD drug development.

Suzanne Farley

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