NEURODEGENERATION

Export disrupts transport

In many demyelinating diseases neurons show axonal damage and impaired axonal transport. However, it is not established whether there is a causal link between the two and what the molecular mechanism underlying such a link might be. Kim *et al.* now show that transport of histone deacetylase 1 (HDAC1) from the nucleus to the cytosol disrupts axonal transport, thereby inducing axonal damage.

The authors detected HDCA1 in the cytoplasm of neurons from mice with cuprizone-induced demyelination, in post-mortem brain tissue from patients with multiple sclerosis and in demyelinated cerebellar slice cultures. They also exposed primary neuronal cultures to glutamate and tumour necrosis factor (TNF) to mimic the inflammatory environment of multiple sclerosis brains. In this case HDAC1 was initially localized in the nucleus; shortly after TNF exposure it moved to the cytosol, was distributed along the length of the neurites and eventually formed aggregates within neurite 'beads', which are early hallmarks of axonal damage. This suggested that nuclear export of HDAC1 into the cytosol might be part of the mechanism that leads to axonal dysfunction.

Neurite beading has been associated with disrupted axonal transport of proteins and organelles such as mitochondria. In neurons treated with glutamate and TNF, axonal transport began to slow down only once HDAC1 became detectable in neurites, and transport slowed down even more when neurite beads began to appear. Thus, the nuclear export of HDAC1 preceded the impairment of axonal transport, which in turn preceded localized beading.

What induces the nuclear export of HDAC1? The authors showed that leucine-rich motifs in HDAC1 bind exportin 1 (CRM1), resulting in HDAC1 transport through the nuclear pore. Indeed, 5 minutes after treating cultures with glutamate and TNF, complexes between CRM1 and HDAC1 began to form. Moreover, inhibiting CRM1-dependent transport prevented HDAC1 export into the cytosol and inhibited both neurite beading and the impaired axonal transport of mitochondria. This shows that in this model HDAC1 nuclear export is required for axonal damage to occur.

These observations suggested that inhibiting cytosolic HDAC1 might improve axonal transport. Indeed, axonal transport of mitochondria was increased in the presence of the HDAC inhibitor MS-275. The authors also showed that HDAC1 in the cytosol must bind to the kinesin motor proteins KIF2A and KIF5 to affect axonal transport. In untreated cells, the cargo protein dynamin formed complexes with KIF2A, KIF5 and α-tubulin, but this was disrupted in cells treated with glutamate and cytokines; MS-275 treatment subsequently restored complex formation.

These findings show that cytokines and excitotoxic amino acids together induce nuclear export of HDAC1. By binding motor proteins, cytosolic HDAC1 disrupts axonal transport of mitochondria. This might result in impaired energy supply to the axon and eventually lead to axonal damage, suggesting that cytosolic HDAC1 might be a potential target for designing treatment for various demyelinating disorders.

Leonie Welberg

ORIGINAL RESEARCH PAPER Kim, J. Y. *et al.* HDAC1 nuclear export induced by pathological conditions is essential for the onset of axonal damage. *Nature Neurosci.* 27 Dec 2009 (doi: 10.1038/nn.2471)