NEURODEGENERATIVE DISEASE

The stress of misfolding

The build-up of misfolded α-synuclein is linked to neurodegeneration in Parkinson's disease and other so-called α-synucleinopathies, but how α-synuclein triggers neuronal death *in vivo* is unclear. Together, two studies from Lee and colleagues show that endoplasmic reticulum (ER) stress contributes to α-synuclein-linked neurodegeneration in mice, and that oligomeric species of α-synuclein may have a role in the induction of such stress.

The accumulation of unfolded or misfolded proteins in cells causes ER stress that can induce the unfolded protein response (UPR). The UPR aims to protect against the toxic accumulation of such proteins, partly through the elevation of chaperone protein expression. Previous *in vitro* studies have shown that high levels of α-synuclein can induce ER stress.

The two new studies used the A53TαSTg mouse model of α-synucleinopathy, in which mice express a human-disease-linked variant of α-synuclein, to reveal that mutant α-synuclein expression is also associated with ER stress *in vivo*. The authors showed that, in these mice, the expression of various UPR-linked chaperone proteins increased with disease progression in the spinal cord and the brain stem — two CNS regions that showed notable α-synuclein-linked pathology.

Activation of the UPR is associated with the phosphorylation of eukaryotic translation initiation factor 2α (EIF2α), which confers a general inhibition of protein translation and is thought to protect cells against an ER stress-induced cell death cascade. Interestingly, no rise in phosphorylated EIF2α levels could be detected in spinal cord samples from A53TαSTg mice, indicating that neurons in these mice may be vulnerable to ER-stress-triggered cell death.

CORBIS

Confocal microscopy revealed that, in A53TαSTg mice, chaperone protein expression was higher in neurons exhibiting α-synuclein pathology than in those without such pathology. Moreover, immunoelectron microscopy revealed that, in pathology-affected neurons, abnormal α-synuclein expression was detectable on the ER membranes, and the ER itself was morphologically abnormal. In biochemical experiments, the authors found that A53TαSTg brain-derived microsomes, which were formed from fragments of ER, were enriched with α-synuclein monomers, aggregates and oligomers, which have been implicated in the pathogenesis of α-synucleinopathies *in vitro*. Thus, α-synuclein pathology seems to be intimately linked with abnormalities in the ER in A53TαSTg mice.

To directly probe whether ER stress has a mechanistic role in α-synuclein-associated neurodegeneration, the authors treated A53TαSTg mice with salubrinal, which inhibits EIF2α dephosphorylation and hence protects cells against chronic ER-stress-induced cell death. Salubrinal treatment did not affect α-synuclein expression but did reduce the accumulation of α-synuclein monomers, oligomers and aggregates in microsomes. Such treatment also delayed the onset of the motor symptoms observed in these mice and increased their lifespan. Thus, salubrinal may protect against α-synuclein pathology-associated ER stress by decreasing the build-up of α-synuclein species in the ER.

Together, these studies provide evidence that α-synuclein-induced ER stress has a crucial role in promoting neurodegeneration in α-synucleinopathies, and that targeting chronic ER stress may represent a plausible target for future therapies. These studies also provide further evidence that oligomeric species of α-synuclein may be neurotoxic.

Darran Yates,
Nature Reviews Neuroscience

This article originally appeared in *Nature Rev. Neuro.* (doi:10.1038/nrn3235).

ORIGINAL RESEARCH PAPERS Colla, E. *et al.* Endoplasmic reticulum stress is important for the manifestations of α-synucleinopathy *in vivo*. *J. Neurosci.* **32**, 3306–3320 (2012) | Colla, E. *et al.* Accumulation of toxic α-synuclein oligomer within endoplasmic reticulum occurs in α-synucleinopathy *in vivo*. *J. Neurosci.* **32**, 3301–3305 (2012)