NEURODEGENERATIVE DISEASE

# Understanding and preventing total catastrophe

Polyglutamine diseases are progressive neurodegenerative diseases characterized by the presence of extended CAG repeats in specific genes, such as ataxin 1; these repeats lead to the generation of polyglutamine-expanded (polyQ) proteins. The mechanism by which polyQ proteins cause disease is not known. One study now shows that polyglutamine expansion affects the binding of the protein to its partners, leading to gain of function or loss of function of the protein's various complexes. Two further reports explore treatment strategies that focus on promoting the degradation of polyQ proteins by the proteasome pathway.

ImageSource

In recent years, several mouse models have been established for spinocerebellar ataxia type 1 (SCA1), in which polyQ-ataxin 1 is expressed in specific subsets of neurons. Furthermore, expression of human polyQ-ataxin 1 in retinal neurons of *Drosophila melanogaster* has provided a different model of SCA1 that allows easy monitoring of retinal degeneration.

Zoghbi and colleagues set out to identify and characterize binding partners of ataxin 1 using a yeast two-hybrid screen, and identified RNA-binding motif 17 (RBM17). Loss of one RBM17 allele partially suppressed retinal decline in the *D. melanogaster* model of SCA1, whereas co-expression of human or *D. melanogaster* RBM17 and polyQ-ataxin 1 worsened neurodegeneration, suggesting that the polyQ-ataxin 1/RBM17 complex confers toxicity and contributes to the neuropathology of the disease.

The authors investigated the nature of ataxin 1 protein complexes in the cerebellum of wild-type and SCA1 mice using gel-filtration chromatography. Polyglutamine expansion of ataxin1 strongly promoted the formation of ataxin 1/RBM17 complexes, whereas formation of a complex of ataxin 1 and capicua, a previously identified binding partner, was attenuated. These data suggest a model of SCA1 neurodegeneration in which gain of function of a particular endogenous protein complex occurs simultaneously with the loss of function of another endogenous protein complex.

Boosting the ubiquitin–proteasome pathway to promote the degradation of polyQ proteins might prevent their accumulation and render affected neurons viable. A protein called CRAG has been shown to facilitate the degradation of polyQ aggregates by the ubiquitin–proteasome pathway. Hirai and colleagues injected lentiviral vectors expressing wild-type CRAG into the cerebellum of polyQ-protein-expressing mice and found that the number and size of the inclusions that characterize the progression of the disease were significantly decreased after CRAG treatment.

Bellen, Zhai and colleagues investigated whether the neuroprotective function of NMNAT (NAD synthase nicotinamide mononucleotide adenylyltransferase) can be harnessed to potentially treat SCA1. They overexpressed NMNAT in the *D. melanogaster* SCA1 model and showed that neurodegeneration was suppressed. In cell culture experiments with various NMNAT enzyme-inactive mutants, they determined that, independent of its NAD synthase activity, NMNAT has a chaperone activity that promotes the degradation of polyQ-ataxin 1 by the proteasome pathway.

These findings shed light on the mechanism that underlies SCA1 and other polyglutamine diseases and open the door to potential treatment strategies, some of which might involve exploiting targets in the ubiquitin–proteasome pathway.

*Claudia Wiedemann*

**ORIGINAL RESEARCH PAPERS** Lim, J. *et al.* Opposing effects of polyglutamine expansion on native protein complexes contribute to SCA1. *Nature* 12 Mar 2008 (doi: 10.1038/nature06731) | Torashima, T. *et al.* Lentivector-mediated rescue from cerebellar ataxia in a mouse model of spinocerebellar ataxia. *EMBO Rep.* **9**, 393–399 (2008) | Zhai, R. G. *et al.* NAD synthase NMNAT acts as a chaperone to protect against neurodegeneration. *Nature* 16 Mar 2008 (doi: 10.1038/nature06721)