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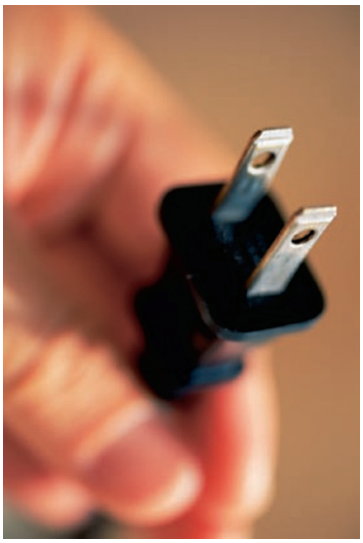
HUMAN DISEASE

A two-pronged model of polyglutamine disease

Polyglutamine diseases are dominant neurodegenerative disorders caused by expansion of unstable CAG repeats in coding regions of a number of genes. Although this polyglutamine expansion is responsible for the toxic properties of the mutant protein, the mechanism that underlies pathology has remained elusive. Focusing on spinocerebellar ataxia type 1 (SCA1), Lim *et al.* show that polyglutamine expansion in the ataxin 1 protein (ATXN1) affects which multiprotein complexes it predominantly associates with. Whereas association of ATXN1 with one complex causes disease by a gain-of-function mechanism, its decreased association with another complex contributes to disease by a loss-of-function mechanism.

Previous studies in SCA1 and Huntington disease indicated that protein domains outside the expanded glutamine region have an important role in pathology, as does interplay between the function of wild-type and mutant protein forms. To investigate this further Lim *et al.* used a number of biochemical approaches in mouse and human cells to look for proteins that interact with ATXN1. In this way, they identified RNA-binding motif protein 17 (RBM17), a protein that preferentially associates with a form of ATXN1 in which polyglutamine tracts have been expanded but that is also phosphorylated at serine 776, which lies outside the polyglutamine tract. The authors suggest that polyglutamine-tract expansion affects the conformation of the C-terminal region of ATXN1, thereby enhancing its interaction with RBM17.



Next, the authors tested the physiological relevance of this protein–protein interaction using a *Drosophila* model of SCA1 in which a human ATXN1 with an expanded polyglutamine tract causes an eye phenotype. Genetic manipulation of *Drosophila* or human RBM17 levels indicated that this protein has an essential role in mediating the polyglutamine-related toxicity.

Further biochemical analysis revealed that ATXN1 and RBM17 interact as part of large protein complexes. Importantly, the proportion of RBM17 in these complexes is increased if ATXN1 contains expanded polyglutamine repeats. But ATXN1 is also found in large protein complexes that contain another protein — capicua homolog protein (CIC); however, the two types of protein complex seem to be distinct and the authors show that RMB17 and CIC compete for ATXN1 interaction.

Given that polyglutamine expansion favours the association of ATXN1 with RBM17, the authors reasoned that this protein might preferentially associate with mutant ATXN1, leaving wild-type ATXN1 to interact with CIC. The authors propose that SCA1 might be caused not only by dominant effects of toxic mutant RBM17-associated ATXN1, but also by loss of protective wild-type ATXN1 that is associated with CIC — in heterozygous patients or animal models the levels of wild-type ATXN1 are reduced by half in comparison with wild-type homozygotes. The authors showed that, in *Drosophila*, increasing RBM17 enhances polyglutamine-mediated toxicity, whereas previous work from the same group showed that increasing CIC represses it. Here, the authors use mouse genetics to show that wild-type ATXN1 is indeed protective and that its loss exacerbates the SCA1 phenotype.

The authors propose that this two-pronged model of SCA1 might also apply to other dominant neurodegenerative diseases, including prion diseases and Alzheimer disease, as well as other polyglutamine diseases.

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ORIGINAL RESEARCH PAPER Lim, J. *et al.* Opposing effects of polyglutamine expansion on native protein complexes contribute to SCA1. *Nature* 12 Mar 2008 (doi:10.1038/nature06731)
FURTHER READING Gatchel, J. R. & Zoghbi, H. Y. Diseases of unstable repeat expansion: mechanisms and common principles. *Nature Rev. Genet.* **6**, 743–755 (2005) | Pearson, C. E. *et al.* Repeat instability: mechanisms of dynamic mutations. *Nature Rev. Genet.* **6**, 729–742 (2005)