REPEAT INSTABILITY

A non-repeat performance

Proteins that contain expanded glutamine repeats are toxic to cells and lead to neurodegenerative diseases in humans — but the repeats themselves might not be entirely to blame. A study in flies and mice shows that the neuronal toxicity seen in one type of ataxia is caused by an interaction between sequences outside the glutamine tract and a protein that is involved in neuronal survival.

Spinocerebellar ataxia 1 (SCA1) is caused by the expansion of a polyglutamine (polyQ) tract in the human ataxin 1 gene (*ATXN1*). The associated neuronal degeneration involves a gain-of-function mechanism. However, it does not simply involve the polyQ repeats, as a version of *ATXN1* that does not have a pathological number of repeats causes neuron loss when it is overexpressed in mice and flies. The fact that polyQ-expanded ATXN1 and its fly homologue ATX1 (which lacks a polyQ stretch) have similar phenotypes when overexpressed in *Drosophila melanogaster* meant that the authors could use the fly system as a starting point for identifying the sequences that are required for SCA1 pathogenesis and the proteins that they bind to.

Biochemical and two-hybrid data revealed that fly and human ataxin 1 bind to Senseless (SENS), a transcription factor that is involved in sensory organ development in the fly, and that the interaction involves a conserved 110 amino-acid domain (AXH) of ataxin 1. Genetic interaction studies supported the physical binding experiments and also showed that fly and human ataxin 1 cause the cell-autonomous degradation of the SENS protein. So, although the polyQ domain is not directly toxic to cells, this domain might stabilize ataxin 1 and allow it to degrade SENS and disrupt its function in sensory organ formation. A similar process occurs in mice, where human ATXN1 interacts with the mouse homologue of SENS, GFIL, through the AXH domain. In fact, in mice the destabilization of GFIL caused by *ATXN1* overexpression leads to the loss of the specific neuronal types (Purkinje cells) that degenerate in patients with SCA1.

This work brings us closer to understanding how ATXN1 causes neurodegeneration. What is true for SCA1 might be true for the other eight or so polyQ-repeat-induced diseases, so studying the wild-type function of these proteins and their cellular interactions could be a fruitful strategy for identifying their pathological basis.

Tanita Casci

References and links

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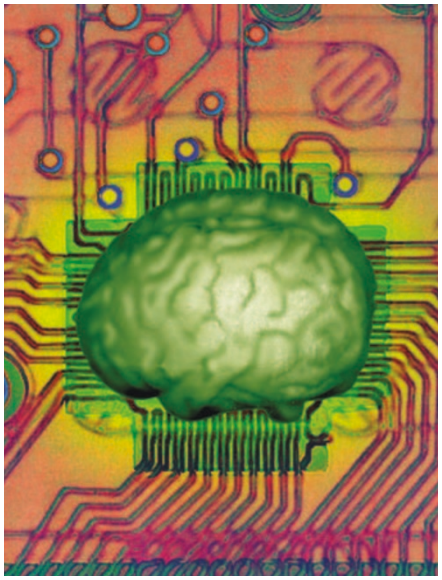
DISEASE MODELS

Constructive connections



Diseases that occur in familial and sporadic forms present serious challenges to researchers, but lend themselves to the discovery of common biological pathways. This situation is exemplified by recent work on a fly model of Parkinson disease (PD), which has revealed a genetic link between the familial and sporadic forms of the disease.

The authors were drawn to a particular gene, *DJ1*, by its involvement in the familial form of PD, and went on to identify two close gene homologues in *Drosophila melanogaster* (*DJ1α* and *DJ1β*). Flys in which one or both of these genes were knocked out were viable and fertile; however, those that were exposed to toxins that influence sporadic PD — such as the herbicide paraquat and the insecticide rotenone — were strikingly more sensitive than normal animals. It's as though a lack of *DJ1* — in particular *DJ1β* — renders organisms more susceptible to environmental toxins, leading ultimately to more rapid death, just as in sporadic PD in humans. DJ1β also shifts to a more acidic form on exposure to these toxins; this isoform might therefore directly influence DJ1 activity, setting up further research that could shed light into mechanisms of DJ1 anti-oxidant function.

This work reinforces the usefulness of animal models for studying gene and environment interactions in human disease and proposes DJ1 as an attractive drug target, given that the same pathway is probably involved in both forms of PD. It also sets out goals for more research into this biological pathway — including resolving potential interactions between the two DJ1 isoforms in protection from toxins, as described in an accompanying paper by Menzies and colleagues.

Tanita Casci

References and links

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FURTHER READING Menzies, F. M. *et al.* Roles of *Drosophila* DJ-1 in survival of dopaminergic neurons and oxidative stress. *Curr. Biol.* **15**, 1578–1582 (2005)

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