tion status may also contribute to toxicity in SCA1 through altered interactions with other proteins[5,6].

Though our understanding of the molecular basis of the polyglutamine disorders has advanced, no effective therapy has emerged. For this reason, approaches that do not require a full understanding of the pathogenesis are attractive. Inhibition of the coding RNA for a dominant mutant allele should result in reduced levels of the toxic protein; hence the interest in exploiting RNAi as a therapeutic approach. Though promising, the development of RNAi-based therapies will need to overcome many of the same problems faced during the development of other nucleic acid–based approaches[7].

Xia *et al.* overcame one common problem by successfully moving cell culture–based results into a relevant preclinical model. The authors used short hairpin RNAs (shRNAs), which are processed intracellularly into small interfering RNAs (siRNAs) of approximately 21 nucleotides. Small interfering RNAs form part of an RNA-protein enzyme complex (RISC) that mediates the degradation of the transcript cognate to the sequence of the siRNA[8]. The authors first assessed potential shRNAs in cell culture, and their work highlights the need to test many RNAi-mediating molecules in culture to ensure efficacy and specificity of RNAi in mammalian cells.

The authors tested the most effective *SCA1* shRNAs in young SCA1 transgenic mice. The degenerative process appeared to slow in these mice, although only an estimated 5–10% of Purkinje cells were transduced. Indeed these effects are even more striking when one considers that RNAi induced only an estimated 60–80% reduction in *SCA1* RNA levels in successfully transduced cells, implying that incomplete gene silencing is sufficient for other cellular processes to cope with the remaining mutant protein.

What needs to happen before RNAi approaches head to clinical trial for dominant genetic disorders such as SCA1? Mice with established neuropathology should be tested to ask whether RNAi can slow neurodegeneration once initiated. As RNAi against the *SCA1* transcript will target both the mutant and normal transcripts, the effect of downregulating the normal protein also needs further evaluation, especially since ataxin-1 knockout mice show some neurological dysfunction. The RNAi approach, however, might offer an advantage here by reducing, not eliminating, protein. Thus, the neurotoxic effect of the mutant protein may be restricted while allowing sufficient wild-type protein to remain for normal function. Additional testing will also be required to see if this RNAi effect can be induced in other brain regions and neuronal types, including the inferior olive and Pontine nuclei, also affected by neurotoxicity in individuals with SCA1.

An important issue in the long term will be the method for delivery of any RNAi effector molecule into the brain. In this study the authors chose an AAV vector because it efficiently transduces a broad range of cell types, particularly neurons, and it expresses transgenes over a long period. To date AAV vectors have been tested mainly in clinical trials to treat cystic fibrosis and hemophilia B. These trials have shown modest efficacy[9], but they have also raised safety concerns because of the detection of vector sequences in semen[9] and transient immune responses in hemophilia B patients (K. High, Howard Hughes Medical Institute, the Children's Hospital of Philadelphia, personal communication). Ongoing trials of AAV delivery of transgenes to the brain in individuals with Parkinson disease and Alzheimer disease[10] may help to realistically assess the feasibility of moving forward with the RNAi approach presented by Xia and colleagues.

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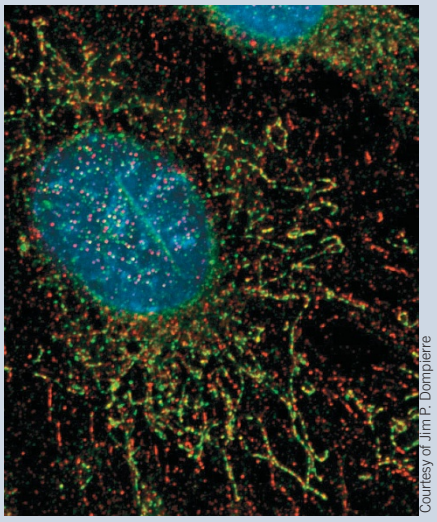
Tracking down huntingtin

Mutations in just one gene, encoding the protein huntingtin, underlie Huntington disease, but the pathogenic mechanisms are unclear. Two recent studies dissect the molecular underpinnings of this polyglutamine disorder.

In the 9 July 2004 issue of *Cell* (**118**, 127–138), Laurent Gauthier and Bénédicte Charrin *et al.* examine whether the disease is caused by the loss of huntingtin function. They find that the wild-type protein enhanced the microtubule-mediated transport of a molecule that supports neuronal survival, brain-derived neurotrophic factor (BDNF; huntingtin in red, BDNF in green in the figure). This effect involved interactions of huntingtin with huntingtin-associated protein (HAP-1) and the molecular motor dynactin. The authors showed that mutant huntingtin failed to transport BDNF properly along nerve fibers, leading to neuronal cell death. Previous work had implicated huntingtin in neuronal survival; this work fleshes out the mechanism.



Courtesy of Jim P. Dompierre

In the 2 July 2004 issue of *Molecular Cell* (**15**, 95–105), Gregor Schaffar and Peter Breuer *et al.* examine whether the pathogenic mechanism depends on the toxicity of the mutant huntingtin. They report that expanded polyglutamine repeats in mutant huntingtin inhibit the function of a native polyglutamine repeat–containing protein, the transcription factor TBP. Polyglutamine repeats in Huntington disease and related disorders have a reputation for affecting native polyglutamine-containing proteins; this could happen by sequestration in polyglutamine-containing nuclear inclusions. Instead, the authors found that the repeats interacted with TBP independent of the formation of insoluble aggregates, and that the HSP70/HSP40 molecular chaperones interfered with this process. As both studies were performed in culture, the relative contribution of these phenomena to disease remains to be established *in vivo*.

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