NEURODEGENERATIVE DISEASE

Antisense targets faulty Huntington allele

Nucleic acid antisense oligomers can discriminate between mutant and wild type ataxin 3 and huntingtin protein expression in cultured cells, suggesting new treatment options for the hereditary disorders Machado–Joseph disease (MJD) and Huntington disease (HD). The faulty allele in both of these genetic traits has strings of extra CAG repeats. These form hairpin structures in the messenger RNA (mRNA), which interfere with normal protein expression. "Our results suggest that these differences in nucleic acid structure can be targets for therapeutic inhibition of gene expression," comments senior author David Corey (University of Texas Southwestern Medical Center, Dallas, TX, USA).

Expanded trinucleotide repeats in the ataxin 3 allele and the huntingtin (*HTT*) gene are at the root of both MJD and HD. Although preventing their expression could theoretically treat both diseases, no means of selectively inhibiting the mutant allele currently exists. Experiments designed by Jiaxin Hu and Masayuki Matsui showed that nucleic acid antisense oligomers can inhibit mutant ataxin 3 and HTT protein expression in cultured cells by preventing translation but not transcription. "Differences in mRNA secondary structure or the number of oligomer binding sites may be important," notes Corey.

> "...differences in nucleic acid structure can be targets for inhibiting gene expression"

The idea of using antisense technology to target expanded CAG repeats was originally suggested to Corey by Ethan Signer from the Hereditary Disease Foundation (New York, USA). "Ethan was wondering whether peptide nucleic acids might offer something to their research portfolio—that gave me the push I needed to focus on HD and huntingtin," says Corey, who regards this as a great example of how a patient advocate can steer research in a productive direction.

"But all we had was a hypothesis until Matsui worked out a method for separating the mutant and wild-type HTT proteins," explains Corey. He also stresses that the selective inhibition achieved is not yet good enough to consider clinical applications. "When a few compounds with the best inhibitory profiles have been identified in cells, we can move onto mouse HD models and then possibly to clinical trials within 2–3 years," he says.

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Original article Hu, J. *et al.* Allele-specific silencing of mutant huntingtin and ataxin 3 genes by targeting expanded CAG repeats in mRNAs. *Nat. Biotechnol.* **27**, 478–484 (2009).