NEURODEGENRATIVE DISEASE

Come on everybody, do the congo!

Doing the congo, rather than the conga, may help you control your body movements, according to new research in the 23 January issue of *Nature*. Junying Yuan and colleagues report that the dye Congo red reduces neuronal dysfunction in a mouse model of Huntington's disease (HD). Although this is exciting research, the dye does not go through the blood– brain barrier and so cannot be used therapeutically in HD.

HD is one of several inherited neurodegenerative disorders characterized by the presence of CAG repeats in DNA, which code for an expanded polyglutamine domain. In the case of HD, the mutated protein is huntingtin. Abnormal polyglutamine proteins form insoluble protein aggregates, which are accompanied by neural dysfunction and cell loss. However, the role of polyglutamine aggregates in neurodegeneration is controversial. Proposed mechanisms for the destructive nature of these diseases have included activation of caspases or other triggers of apoptosis, mitochondrial or metabolic toxicity, and interference with gene transcription.

In order to determine the role played by aggregation in expanded polyglutamine diseases, the authors used the azo dye Congo red, which preferentially binds to the type of β-sheet structures formed in the aggregates, specifically inhibiting aggregation as well as disrupting preformed aggregates. In cultures of cells transfected with constructs encoding expanded polyglutamine repeats the dye prevented cell death, preserved normal cellular protein synthesis and degradation functions, and promoted the clearance of polyglutamine aggregates, compared with untransfected controls. In a mouse model of HD, infusion of Congo red, intraperitoneally or directly into the brain, resulted in the clearance of the repeats and beneficial effects on motor function, weight loss and survival. The effects of the dye were both direct, by inhibiting the ability of aggregates to induce cytotoxic events, and indirect, by increasing the accessibility of remaining aggregates to the degradation machinery of the proteasome.

This finding shows that protein aggregation is crucial to cell death in polyglutamine diseases. Furthermore, it also supports the idea that preventing polyglutamine aggregation is a useful therapeutic approach to controlling these diseases.

Melanie Brazil

References and links

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WEB SITE

Encyclopedia of Life Sciences: http://www.els.net Huntington disease

STRUCTURE-BASED DRUG DESIGN

An ACE surprise

Since the 1980s, inhibitors of angiotensin converting enzyme (ACE inhibitors) have achieved great success as first-line therapy for cardiovascular and renal disorders, such as hypertension, myocardial infarction and diabetic neuropathy. But what is perhaps more remarkable is the fact that ACE inhibitors were successfully developed with no knowledge of the enzyme's structure, and were designed on an assumed mechanistic homology to carboxypeptidase A.

Now, Acharya and colleagues have filled in the missing gaps in our knowledge by determining the X-ray structure of ACE, and its complex with the widely used ACE inhibitor lisinopril, at high resolution. There are two isoforms of ACE (somatic and testicular), but the authors looked at the shorter testicular version, which contains a carboxy-terminal (C) domain (the somatic form contains a C and an amino-terminal (N) domain), as previous evidence suggested that the C domain is the dominant functional site.

The three-dimensional structure revealed that ACE in fact bears little resemblance to carboxypeptidase A (except the active site zinc-binding motif). Instead, it resembles rat neurolysin and *Pyrococcus furiosus* carboxypeptidase, despite sharing little amino-acid-sequence similarity to these two proteins. This similarity extended to the active site, which consists of a deep, narrow channel that divides the molecule into two subdomains. On top of the molecule is an amino-terminal 'lid', which seems to allow only small peptide substrates (25–30 amino acids) access to the active site cleft — this accounts for the inability of ACE to hydrolyse large, folded substrates. Current ACE inhibitors bind to both the C and N domains, so this detailed view of the active site should provide an opportunity to design next-generation, domain-selective ACE inhibitors with the potential for greater efficacy, fewer side effects and new treatment indications.

Simon Frantz

References and links

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