NEURODEGENERATION

Ironing out disease

Many neurodegenerative diseases, including Parkinson's and Alzheimer's, are associated with excessive deposition of iron in the regions of the brain that undergo degeneration. But are these deposits a cause or a consequence of the neurodegenerative process? Two studies published in *Nature Genetics* have set out to find the genetic basis of two diseases that are characterized by a build-up of iron in the basal ganglia, to find out whether the primary cause is a defect in iron metabolism.

Curtis *et al.* have identified a new dominantly inherited, adult-onset disease of the basal ganglia in a family from the north of England. They showed that affected individuals have a mutation in the *FTL* gene, which

encodes one of the subunits of the iron storage protein ferritin. They suggest that this mutation interferes with the stability of the ferritin molecule, causing iron to be inappropriately released into the cell and transported along the axon.

In the case of the second disease, Hallervorden–Spatz syndrome, the effects on iron metabolism are less direct. Zhou *et al.* showed that patients with this recessively inherited movement disorder have a mutation in a gene that they named *PANK2*. This gene encodes pantothenate kinase, an enzyme that catalyses the phosphorylation of vitamin B5. This reaction uses cysteine, so in cells where the enzyme is defective, cysteine tends to

accumulate. Cysteine is known to be a chelator of iron, so the accumulation of iron might be a secondary consequence of raised cysteine levels.

So, both of these diseases seem to be caused by mutations that affect iron storage, and in both cases, it is suggested that the iron deposits cause oxidative damage to axons. These studies show how iron accumulation could be a cause of neurodegeneration, rather than a secondary effect, and it will be interesting to find out whether iron contributes to the aetiology of any other neurodegenerative diseases.

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References and links

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NEURODEGENERATION

Blocking prion conversion

Prion proteins are responsible for the transmissible spongiform encephalopathies, which include scrapie, bovine spongiform encephalopathy and Creutzfeldt–Jakob disease. The pathogenic prion protein (PrP^{Sc}) is believed to interact with the endogenous cellular prion protein (PrP^{C}) and convert it into the pathogenic form. Two groups have recently shown that antibodies against cell-surface PrP^{C} can inhibit the accumulation of PrP^{Sc} in infected cell cultures, and may even clear the infection altogether.

The studies, by Enari *et al.* and Peretz *et al.*, used one of the few cultured cell types that is susceptible to prion infection — the mouse neuroblastoma N2a cell line. Enari *et al.* treated infected cultures with a monoclonal antibody directed against the prion protein, and found that the levels of PrP^{Sc} dropped rapidly, and that treatment with the antibody could also stop uninfected cells from becoming infected. Peretz *et al.* tested a range of Fab fragments — the part of the antibody that binds to the antigen — that recognized

different regions of PrP^{C} , and found that they, too, inhibited prion propagation in the cell cultures. They also showed that the specific region of the prion that is bound by the antibody is important in determining the efficacy of the treatment, which may give important insight into the mechanism of prion propagation.

Both studies showed that after cell cultures were treated with antibodies for two or three weeks, PrP^{Sc} was undetectable in the cultures for several more weeks, indicating that the treatment might have completely cleared the infection. Enari *et al.* also treated their infected cells with phosphatidylinositol-specific phospholipase C (PIPLC), which cleaves PrP^{C} at the cell surface, and found that it had a similar effect to the monoclonal antibody.

The authors of the studies believe that the antibodies work by binding to PrP^{C} , the endogenous prion protein, and thereby prevent PrP^{Sc} from interacting with it. This means that no new PrP^{Sc} can be made, and the existing PrP^{Sc} is rapidly degraded. PIPLC also prevents the interaction

between PrP^{Sc} and PrP^{C} , by cleaving PrP^{C} from the cell membrane.

These results have intriguing parallels with recent demonstrations that antibodies against β -amyloid protein can reduce brain amyloid in a mouse model of Alzheimer's disease. In both cases, much more work is needed before it will be clear whether antibody treatments are likely to be clinically useful — but they certainly represent a promising avenue for investigation.

A third study, by Korth *et al.*, suggests another potential treatment for prion disorders. The researchers found that two existing drugs, quinacrine and chlorpromazine, could inhibit prion replication in the same culture system as used in the antibody studies. Although the mechanism of action of these drugs is unclear, the authors suggest that they could be immediate candidates for treating prion diseases.

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IN THE NEWS

Miracle cure?

BSE and the related human disease, variant CJD, have never been far from the headlines. This month, *The Mail on Sunday* (12 August 2001) reported that a young woman with suspected vCJD had been 'cured' by an experimental treatment from the American group headed by Stanley Prusiner.

Rachel Forber was desperately ill and had been given just months to live. According to the report, her father, a lorry driver from Merseyside, UK, surfed the web to find someone who could help her. Prusiner's team agreed to treat her with drugs that had shown promise in test-tube trials. And 19 days later, Rachel was able to "walk unaided, talk, eat with a knife and fork, and perform coordination tests which before treatment were impossible."

Although initial details were sketchy, the story developed across the media over the following two days. It emerged that the treatment had consisted of two drugs — quinacrine, an antimalarial, and chlorpromazine, which is used to treat schizophrenia. The drugs had been identified as potential therapeutic agents by Carsten Korth in Prusiner's laboratory. He screened existing drugs that were known to cross the blood–brain barrier for their ability to inhibit prion replication in cultured cells.

According to newspaper reports, a full-scale clinical trial is planned. And details of Korth's work appeared in *Proceedings of the National Academy of Sciences* on 14 August, coinciding with the height of the press coverage (see 'Blocking prion conversion' on this page).

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