been optimized and developed into marketed drugs because of the long time-scale of the drug development process. However, CC will remain a very important tool, which will increase knowledge, leading to an easier and faster search for new drugs.

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Rebecca N. Lawrence

β-Sheet breaking peptide might treat prion disease

Although human prion diseases are relatively rare, their effects on patients are devastating and there is currently no available treatment. A group of scientists from Serono Pharmaceutical Research Institute (Geneva, Switzerland), led by Claudio Soto, have now developed a novel peptide that might delay the progression of prion diseases by converting abnormal, destructive prion protein (PrP^{Sc}) back into normal prion protein (PrP^{c})[1].

Conversion of PrP^{c} to PrP^{Sc}

A key event in prion diseases is the conversion of PrP^{c}, a protein that contains many α-helices, into PrP^{Sc}, an isomer that contains a high proportion of β-pleated sheets[2]. PrP^{Sc} is an insoluble protein that is highly resistant to proteolytic digestion; these properties leading to its accumulation, particularly in the brain. Hence, the progression of prion diseases such as Creutzfeldt– Jakob disease (CJD), kuru, Gertsmann–Straussler–Scheiker disease and fatal familial insomnia in humans, and scrapie and bovine spongiform encephalopathy (BSE) in animals, occurs slowly at first but is then relentless.

Soto and colleagues at the New York University Medical Centre (NY, USA) reasoned that it should be possible to design molecules to disrupt the β-sheet-rich segments of PrP^{Sc} to inhibit their aggregation. Initially, they produced short synthetic peptides with sequence homology to PrP in the conserved region spanning residues 115–122, as this region appears to be important for the conversion of PrP^{c} to PrP^{Sc}. One of these peptides, iPrP13 (a 13-residue molecule with the sequence DAPAAPAGPAVPV), could induce the unfolding of the β-sheets and was termed a 'β-sheet breaker peptide'[1].

Effects of the iPrP13 peptide

In preliminary *in vitro* experiments, the protease susceptibility of partially purified PrP^{Sc} from scrapie-infected mouse brain was measured after incubation with different concentrations of iPrP13. Incubated samples showed significantly lower concentrations of the protease-resistant protein, indicating that a proportion of the PrP^{Sc} had been disrupted[1]. The extent of the change was dependent on the concentration of the peptide added; the concentration of protease-resistant prion protein fell from 100% to 49% at a onefold molar excess of iPrP13 but from 100% to 11.5% when a 1000-fold molar excess was used. Chemical analysis of PrP^{Sc} that had been incubated with the breaker peptide revealed a reduction in the β-sheet content of the molecule from 41% to 8% and an increase in the proportion of α-helix and random coil structure (Fig. 1).

When the higher concentration of iPrP13 was incubated with PrP^{Sc} derived from non-murine sources, including from one patient with CJD and one patient with new-variant CJD, a smaller reduction in the concentration of protease-resistant prion protein was seen, but it was still highly significant. 'Further development of β-sheet breaker peptides as therapeutic agents will require closely refining the peptide sequence', says Soto.

Soto then went on to test the iPrP13 peptide in a cellular model of familial prion disease[1]. Chinese hamster ovary cells overexpressing mutated PrP, that has the properties of PrP^{Sc}, were incubated with iPrP13 (100 $\mu g\ ml^{-1}$) for 48 h. When treated cells were exposed to proteinase K, the PrP^{Sc} signal was virtually undetectable, indicating a significant change in the level of PrP^{Sc} expressed. *In vivo* tests in mice infected with a sample containing partially purified PrP^{Sc} that had been pre-treated with an equimolar concentration of iPrP13

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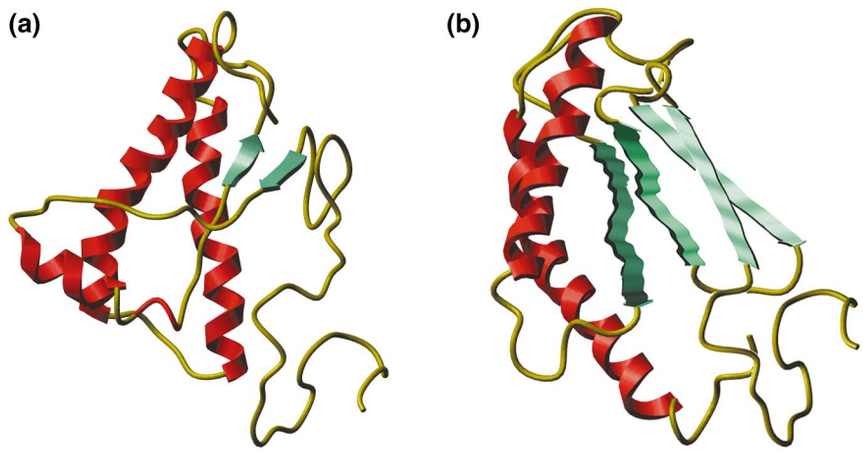

Figure 1. *Computer-generated models for the 3D-structure of PrP^{c} and PrP^{Sc}. (a) This is from the Brookhave Database and shows the structure of PrP^{c}, as determined by NMR. (b) This is a computational model of the structure of PrP^{Sc}. α-Helices are shown in red and β-pleated sheets in green. PrP^{Sc} clearly has a greater proportion of β-sheets, with fewer α-helices than PrP^{c}.*

were less prone to develop scrapie-like symptoms[1]. There was a significant delay in the time-to-onset of symptoms and the quantity of infectious material diminished by 90–95% after incubation with the β-sheet breaker peptide.

'Although we are still at an early stage of development, this is a promising putative treatment for prion disease', claims Soto. One of the key researchers in this field, Adriano Aguzzi (University Hospital of Zurich, Switzerland), agrees: 'This study is very preliminary because adding a drug to the infectious agent before infection is not really a therapy. However, the experiments are sound and well controlled and this is an exciting breakthrough.' Soto's team is also planning to investigate the effect of administering the peptide to mice after they have been inoculated with PrP^{Sc}. 'The demonstration that the β-sheet breaker peptide can provide post-exposure prophylaxis will be crucial', says Aguzzi.

Although various small molecules, such as polyanions, have delayed the appearance of symptoms in laboratory animals infected with scrapie, their mechanism of action is unknown[3]. These compounds are also generally highly toxic, making them unsuitable as drug candidates. Peptides are more acceptable as drug candidates, but they are quickly degraded by enzymes and are difficult to get across the blood–brain barrier. 'These problems have been previously solved for other peptides and we are making good progress with this one', reports Soto.

Future studies

Although it will be at least two or three years before iPrP13 can enter Phase I clinical trials, Aguzzi predicts this approach might have implications for many more patients than the few currently affected by prion diseases. 'Every day that passes without signs of an increase in the number of cases of new-variant CJD is good, but an epidemic of hundreds-of-thousands of cases is still not impossible.'

Aguzzi also stresses that any therapy for CJD must be given at an early enough stage to prevent the onset of neurodegeneration. Abnormal prion protein accumulates in the periphery for a long time before it crosses the blood–brain barrier and causes brain plaques. Blocking the disease at this stage would be feasible but would require a reliable test to identify those at risk. 'I hope that this study will provide a new impetus for research into prion disease diagnosis and therapeutics. We cannot adopt a "wait-and-see" approach; we must work now so that we can be prepared for the worst', concludes Aguzzi.

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Kathryn Senior

Collaboration...

Medarex (Princeton, NJ, USA) has formed a strategic alliance with **Regeneron Pharmaceuticals** (Tarrytown, NY, USA) to discover, develop and commercialize human antibodies as therapeutics. More than 20 initial targets have been selected, including growth factors, cytokines and receptors, and more targets are anticipated in the future. The collaboration will involve the use of Medarex's HuMAb–Mouse technology together with Regeneron's target identification expertise and related technologies. Under the terms of the agreement, both companies will share preclinical and clinical development responsibilities, as well as any subsequent marketing necessary from the development of successful therapies.