Three-dimensional NMR structure of a self-folding domain of the prion protein PrP(121–231)

In the 1996 December issue of *TiBS*, S. B. Prusiner published a comprehensive review on the 'molecular biology and pathogenesis of prion diseases'[1]. In a discussion on the molecular basis of the 'protein-only' hypothesis[2,3], which assumes that the prion protein, PrP, can adopt a benign 'cellular' conformation, PrP^{C}, and a pathogenic 'scrapie' form, PrP^{Sc}, frequent reference was made to a previously published theoretical model[4] of the three-dimensional structure of a carboxy-terminal domain of PrP^{C}. The experimental three-dimensional structure of a related carboxy-terminal domain of PrP^{C}, PrP(121–231) (Fig. 1a), has recently been determined by nuclear magnetic resonance (NMR) spectroscopy[5], and was found to have a different molecular architecture from that obtained through the theoretical prediction. Therefore, as a service for the readers of *TiBS*, we feel that we should point out some implications of this experimentally determined structure.

PrP(121–231) is an intrinsically stable domain of PrP that folds autonomously and reversibly *in vitro*[6]. It contains all residues with post-translational modifications as in mature PrP^{C} (Ref. 7), as well as most of the point-mutation sites that have been associated with inherited human prion diseases[1] (Fig. 1). PrP(121–231) also represents the bulk of the segment 81–231, which has been reported to be sufficient for the generation and propagation of infectious prions *in vivo*[8]. In addition, preliminary NMR data on the intact amino acid sequence of PrP^{C} (residues 23–231) indicate that its segment 121–231 has the same fold as that of PrP(121–231) (R. Riek *et al.*, unpublished).

The three-dimensional structure of mouse PrP(121–231) contains three α-helices and an antiparallel β-sheet[5]. The β-sheet might be a nucleation site for the conformational transition to the infectious, oligomeric form of the prion protein, PrP^{Sc}, for which an increased content of β-sheet structure is expected[9]. In addition, a group of amino acids that have been proposed to be important for the species barrier of prion disease transmissions[10,11] are clustered within or adjacent to helix 1 of PrP(121–231). This helix, which is relatively isolated from the core of the structure (Fig. 1a), might thus be part of a PrP^{Sc}-binding site in PrP^{C} (Ref. 5).

As the residues concerned are all identical in the prion proteins from mouse and human origin[12], the structure

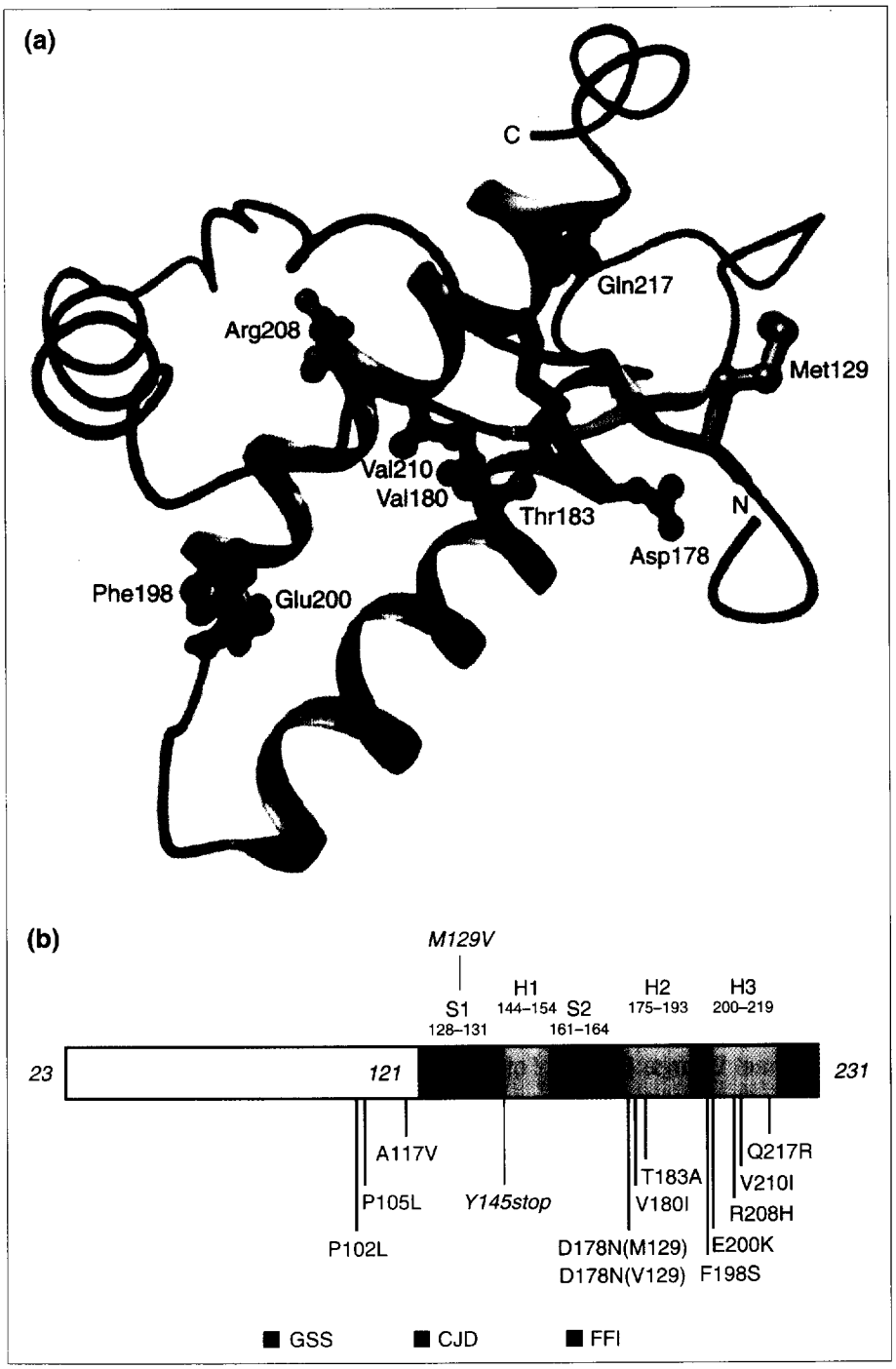

Figure 1

(a) Ribbon diagram of the NMR structure of mouse PrP(121–231)[5] and location of the point mutation sites that have been related to inherited human prion diseases. The three helices (yellow), the antiparallel, two-stranded β-sheet (cyan), the connecting loops (green), and the single disulfide bond between Cys179 and Cys214 (dark grey) are indicated. The side-chains in the mutation sites that have been linked to inherited Creutzfeldt–Jakob disease (CJD), the Gerstmann–Sträussler–Scheincker syndrome (GSS) and fatal familial insomnia (FFI) are given in blue, red and pink, respectively. The sidechain of Met129, i.e. the polymorphism site in human PrP, is shown in light grey. The figure was generated with the program MOLMOL[15]. **(b)** Sequence locations of all regular secondary structures in PrP(121–231)[5] and locations of point mutations that have been associated with inherited human prion diseases[1]. PrP(121–231) (grey) comprises the carboxy-terminal 111 residues of mature mouse PrP^{C} (residues 23–231; residue numbering according to human and hamster PrP^{12}). The positions of the three α-helices (H1–H3) and both strands of the antiparallel β-sheet (S1, S2) in the NMR structure of PrP(121–231) are indicated (regular secondary structures are numbered according to their appearance in the sequence). Amino acid exchanges in mature human PrP, which have been associated with inherited CJD, FFI and GSS[1], are shown in the lower part of the figure. All these residues are identical in both wild-type human and mouse PrP (Ref. 12). The polymorphism at residue 129 in human PrP, which determines the phenotype of diseases that have been linked to the D178N mutation[13], is indicated above the sequence.

of mouse PrP(121–231) allows a detailed analysis of the effects of nearly all point-mutations in human PrP that have been linked with inherited prion diseases, such as the Creutzfeldt–Jakob disease (CJD), the Gerstmann-Sträussler-Scheincker syndrome (GSS) and fatal familial insomnia (FFI)[1] (Fig. 1b). The eight mutation sites contained in PrP(121–231) are all located either within or immediately adjacent to helix 2 and helix 3, which form the scaffold of the structure of PrP(121–231). Point mutation sites associated with inherited CJD or inherited GSS are not clustered in the structure of PrP(121–231) (Fig. 1). The NMR structure also shows that the polymorphism at residue 129 in human PrP (Met or Val), which is located in the first β-strand and determines the phenotype of the disease linked with the D178N mutation[13], is not in direct contact with Asp178 (Fig. 1a).

Overall, the experimental three-dimensional structure of PrP(121–231) provides a platform for attempts to rationalize previously advanced suggestions that inherited prion diseases might be linked to reduced stability of the PrP^C form of the mutant proteins[4,14]. In addition, it also provides a rational basis for the investigations of the species barrier of prion disease transmission at the molecular level.

Acknowledgements

This project was supported by the Schweizerischer Nationalfonds (Project 31.32035.91) and the ETH Zürich. S. H. was supported by the Boehringer-Ingelheim-Fonds.

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Election of Fellows to The Royal Society

On 15 May 1997, 40 new Fellows and six new Foreign Members were elected to the Society. Election to the Fellowship is recognized worldwide as a sign of the highest regard in science. We are pleased to congratulate the following people who have made outstanding contributions to biochemistry, molecular biology and medicine.

Dr Christopher Michael Bate. Reader in the Dept of Zoology, University of Cambridge, UK.

Dr Michael George Bulmer. Formerly Professor in the Dept of Biological Sciences, Rutgers University, New Jersey, USA.

Professor Christopher David Garner. Professor of Inorganic Chemistry, University of Manchester, UK.

Professor James Julian Bennett Jack. Professor of Cellular Neuroscience, University of Oxford, UK.

Dr Philippa Charlotte Marrack. Member in the Dept of Medicine, National Jewish Medical Research Center, Colorado, USA; and Investigator, Howard Hughes Medical Institute, Chevy Chase, USA.

Professor Timothy John Mitchison. Professor in the Dept of Pharmacology, University of California, San Francisco, USA.

Professor Richard Graham Michael Morris. Professor of Neuroscience, University of Edinburgh, Scotland, UK.

Professor Kenneth Bannerman Milne Reid. Director of the MRC Immunochemistry Unit, University of Oxford, UK.

Professor Alan Bernard Rickinson. Professor and Head of Cancer Studies in the University of Birmingham, UK.

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Professor Robin Anthony Weiss. Professor of Viral Oncology at the Institute of Cancer Research, London, UK.

Dr Richard Dean Wood. Principal Scientist at the Imperial Cancer Research Fund, South Mimms, UK.

Professor Walter Jakob Gehring. Professor of Cell Biology in the University of Basel, Switzerland.

Professor Stanley Ben Prusiner. Professor of Neurology and of Biochemistry and Biophysics in the University of California School of Medicine, San Francisco, USA.