Molecular Psychiatry (1998) 3, 196–197

NEWS & VIEWS

Can loss-of-function prion-related diseases exist?

Discovery of mutations of the PrnP gene without typical plaque formation and the characterization of two prion receptors led us to postulate a new class of prion-related disease: 'loss of function'.

Recently we have described a point mutation (N171S) in the prion protein gene in a family with psychiatric illness.[1] Previously an identical mutation was reported in a normal control of a study concerning Creutzfeld–Jakob disease (CJD).[2] We have not provided formal proof of a link between this mutation and the etiology of the psychiatric diseases displayed by this family. On the other hand, finding the mutation in five of six affected and in only one of six normal siblings is suggestive of at least some involvement of a polymorphism at position 171 in an inherited susceptibility to a still unknown genetic or epigenetic etiological agent. A similar scenario was depicted for the polymorphism encountered at position 129 of the PrnP gene, allelic homozygosity of which predisposes either to Gerstmann–Straussler Scheinker or to Familial Fatal Insomnia.[3] Other genetic lesions of the PrnP gene have been reported which lead to initially psychiatric disorders eventually evolving to classical CJD, with a fatal outcome.[4,5]

The human related prion diseases (PRD) are brought about by conformational changes of the normal cellular sialylated, GPI-anchored prion glycoprotein (PrPc), a cell surface molecule predominantly expressed in the hippocampus and the cerebellum. Such conformational changes can be determined by inherited mutations or by interaction with an already altered prion molecule (PrPsc) which can be acquired by infection.[6]

The conversion from a predominantly alphahelical to a beta-pleated sheet conformation may lead to aggregation and deposition of the altered molecules as cytoplasmic plaques which represent the hallmark of these diseases insofar as anatomopathological findings are considered.[7] The psychiatric disorders displayed by the family that we studied are not characterized by plaque accumulation. However the involvement of the hippocampus is pointed out in schizophrenia. MRI studies have indicated that a significant reduction in size of the temporal lobe, in particular of the hippocampus and the amygdala, may occur.[8] Such findings have been correlated with a decrease in hippocampal neuron size, in particular from the subiculum, and the entorrhinal cortex, in post mortem examinations.[9] Although the physiological role of the PrP protein still eludes us, an indication was provided by studies on hippocampal slices from PrP null mice (in which the PrP gene has been deleted), which display GABA-a receptor mediated fast inhibition and impaired long-term potentiation.[10] Another insight has been provided by the discovery of at least two putative cell surface receptors for PrP.[11,12] It was speculated that the interaction between PrP (itself a cell surface molecule) and such a receptor might promote cell–cell heterophilic interactions necessary to establish neuronal networking.[11] Clearly, mutations in the genes coding for such receptors might also impair such interactions altering PrP function. While plaque-forming PRD can be classified as deposit or storage diseases, a new category of PRD seems to be emerging, in which PrP or PrP receptor mutations lead to functional impairment rather than deposit formation and could therefore be classified as loss-of-function diseases.

HB Samaia[1] and RR Brentani[2]
[1]Department of Psychiatry, UNIFESP, Sao Paulo;
[2]Ludwig Institute of Cancer Research,
Sao Paulo, SP, Brazil 01509-010

Correspondence: Dr RR Brentani, Ludwig Institute of Cancer Research, Rua Prof Antonio Prudente, 109, 4° andar, Sao Paulo, SP, Brazil 01509-010

References

1 Samaia HB, Moura RP, Simpson AJG, Brentani RR. Psychiatric disorders linked to prion mutations. *Nature* 1997; **390**: 241.
2 Fink JK, Peacock ML, Warren Jr JT, Roses AD, Prusiner SB. Detecting prion protein gene mutations by denaturing gradient gel electrophoresis. *Hum Mutat* 1994; **4**: 42–50.
3 Goldfarb LG, Petersen RB, Tabaton M, Brown P, LeBlanc AC, Gambetti P *et al*. Fatal familial insomnia and familial Creutzfeldt–Jakob disease: disease phenotype determined by a DNA polymorphism. *Science* 1992; **258**: 806–808.
4 Collinge J, Brown J, Hardy J, Mullan M, Rossor MN, Baker H *et al*. Inherited prion disease with 144 base pair gene insertion; II: clinical and pathological features. *Brain* 1992; **115**: 687–710.
5 Nitrini R, Rosemberg S, Passos-Bueno MR, da Silva LST, Iughetti P, Papadopoulos M *et al*. Familial spongiform encephalopathy associated with a novel prion protein gene mutation. *Ann Neurol* 1997; **42**: 138–146.
6 Prusiner SB. Molecular biology and pathogenesis of prion diseases. *TIBS* 1996; **21**: 482–487.

7 Prusiner SB. Genetic and infectious prion diseases. *Arch Neuro* 1993; **50**: 1129–1152.
8 Chua SE, McKenna PJ. Schizophrenia—a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. *Br J Psychiatry* 1995; **166**: 563–582.
9 Arnold SE, Franz BR, Gur RC, Gur RE, Shapiro RM, Moberg PJ *et al*. Smaller neuron size in schizophrenia in hippocampal subfields that mediate cortical-hippocampal interactions. *Am J Psychiatry* 1995; **152**: 738–748.
10 Collinge J, Whittington MA, Sidle KCL, Smith CJ, Palmer MS, Clarke AR *et al*. Prion protein is necessary for normal synaptic function. *Nature* 1994; **370**: 295–297.
11 Martins VR, Graner E, Garcia-Abreu J, de Souza SJ, Mercadante AF, Veiga SS *et al*. Complementary hydropathy identifies a cellular prion protein receptor. *Nature Med* 1997; **3**: 1376–1382.
12 Rieger R, Edenhofer F, Lasmezas CI, Weiss S. The human 37-kDA laminin receptor precursor interacts with the prion protein in eukaryotic cells. *Nature Med* 1997; **3**: 1383–1388.