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Prion vaccine: is there hope against CJD?

Josh P. Roberts, freelance writer

There is, to date, no effective way to prevent or treat prion diseases such as Creutzfeldt–Jakob disease (CJD). However, now researchers have shown that it is possible to delay the onset of a prion-based disease in mice, by immunizing with a recombinant protein. But do these findings have any relevance to human CJD?

Biochemist Stanley Prusiner, who won the Nobel Prize for his pioneering research on prions, has speculated that, 'virtually all neurodegenerative disorders involve abnormal processing of neuronal proteins' [1]. If this is true, then insights from recent attempts to treat diseases such as Alzheimer's (AD) – which affects more than four million people in the USA alone – could have a profound bearing on research into other maladies such as prion diseases.

Work in transgenic mouse models of AD has shown that immunizing them with variants of the implicated protein can ameliorate various manifestations of the disease [2]. But other prion diseases – including CJD, scrapie in sheep, bovine spongiform encephalopathy (BSE) in cattle, and chronic wasting disease in deer – have been uniformly untreatable and fatal.

Based on the earlier mouse work on AD, a team from New York University (http://www.nyu.edu) wagered that a similar approach might prove effective in similar neuropathies. Now, in a study published in the *American Journal of Pathology*, neurologist Thomas Wisniewski and his collaborators provide the first report to show any promise of an immunological approach to treating prion diseases [3]. Other approaches thus far have all been limited by toxicity or pharmacokinetic concerns.

Pathogenic proteins

Like other neurodegenerative pathologies, prion diseases are associated with the accumulation of aberrant proteins in the CNS. The plaques blamed for the damage in these diseases are composed of a protein known as PrP^{Sc}, which is believed to 'reproduce' by recruiting normal cellular proteins (known as PrP^{C}) and somehow inducing them to convert to the pathogenic form.

PrP^{Sc} is identical in sequence to PrP^{C}, but it differs in three-dimensional conformation. However, these aberrant proteins do not elicit a classical immune response, presumably because they are not seen as foreign. Wisniewski and colleagues have overcome this obstacle by vaccinating mice with recombinant PrP (recPrP) mixed with a powerful adjuvant: heat-killed mycobacteria. Following inoculation with PrP^{Sc}, mice immunized with the mixture develop prion disease later than unvaccinated controls (Fig. 1). There is a significant correlation between a delay in the onset of disease and a high antibody titer to PrP^{Sc}, especially at higher inoculation doses.

Relevance to humans

Wisniewski is circumspect, however, about the potential of the immunization approach for the direct prevention of prion diseases in humans. 'Down the road, with further development, it might be used as a vaccine, potentially, for human populations [such as] healthcare workers who are at risk of exposure.'

'We need to be very cautious about toxicity,' he added. Immunizing against AD disease has caused encephalitis and meningitis, Wisniewski observed, which should give researchers pause about using similar methods to prevent prion diseases.

However, the work could bear relevance to humans even if it never reaches them directly. Wisniewski says it is reasonable to expect that animal trials could begin in three or four years – perhaps on deer, which, in the western US, have upwards of 40% incidence of chronic wasting disease. There is growing concern that hunters could develop prion-based diseases if they eat meat from deer with the disease.

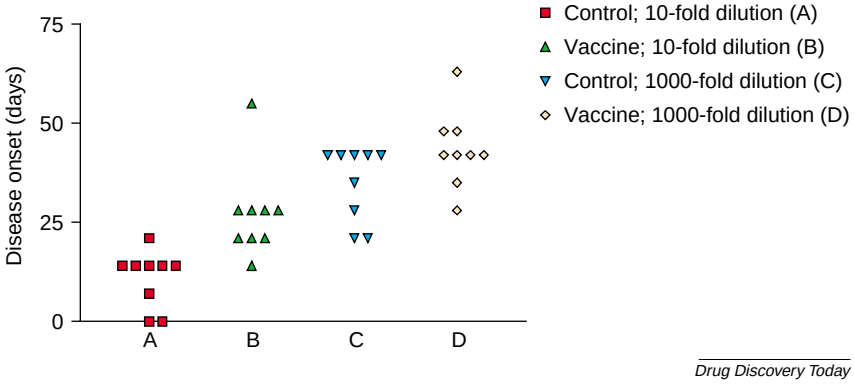

Figure 1. Vaccination with $recPrP^{Sc}$ delays the onset of scrapie in mice. Reproduced, with permission, from ref. [3].

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However, even as a preventive strategy in animals, these results fail to impress another researcher who has studied scrapie and AD. The immunization 'clearly isn't very protective,' comments microbiologist Steven Wietgrefe of the University of Minnesota (http://www.umn.edu). Vaccination, he points out, delayed the onset of disease – which has a normal incubation period of perhaps 175 days – by only about 10 days. 'For protecting deer and elk herds,' he says, 'it probably wouldn't be worth the trouble if the vaccine delays, but does not stop, the infection.'

Future work

The NYU researchers are working towards outright protection. The key, Wisniewski hypothesizes, is higher antibody titers. To this end, they are looking for better adjuvants, using mutated variants of the recPrP vaccine. They hope these variants will elicit a stronger immune response while being less likely themselves to take on the β-pleated sheet conformation characteristic of pathogenic prion proteins.

The group is also trying a variety of multi-faceted approaches, such as passively immunizing some test animals with anti-PrP^{Sc} antibody preparations, and to boost the IgA antibody response, they have begun feeding mice with recPrP. (Subcutaneous immunization induces principally IgG2a and IgG2b.) 'Because scrapie infections often arise in nature via the gut,' Wisniewski reasoned, 'we might be able to hinder penetration of the agent into the body.'

Wietgrefe also voiced concern over the lack of any discernable histopathological difference between the brains of vaccinated versus control animals. This could be because of the assays being conducted only on mice that had reached their clinical endpoint, regardless of how long it took them to get there.

Because of the lengthy clinical incubation period of the disease, scientists in this field must wait nearly six months before they can know whether any treatment (or set of treatments) has had any effect. The NYU researchers are gearing up to address this issue by using magentic resonance imaging (MRI) to assess damage to the brains of inoculated mice, which could appear long before any neurological symptoms become apparent. An added benefit is that this approach requires far fewer mice than histological examinations, because it does not require destroying the animals. Thus it is easier to test several treatments concurrently.

References

1 Prusiner, S. (2001) Shattuck Lecture – Neurodegenerative diseases and prions. *New Engl. J. Med.* 344, 1516–1526
2 Eziri, M.M. (2001) Is an effective immune intervention for Alzheimer's disease in prospect? *Trends Pharmacol. Sci.* 22, 2–3
3 Sigurdsson, E.M. *et al.* (2002) Immunization delays the onset of prion disease in mice. *Am. J. Pathol.* 161,13–17

News in brief

Targets and mechanisms

Leads on drugs for controlling obesity?

Researchers have recently found that the appetite-suppressing drug, fenfluramine, acts by targeting the same brain pathways that control appetite, obesity and anorexia [1]. Such results could lead to the development of selective treatments for effective weight control, particularly for the treatment of obesity.

Researchers from the Beth Israel Deaconess Medical Center, led by Joel Elmquist, studied the effects of D-fenfluramine (D-FEN) in the brains of rats. The drug induces anorexia in the rats and this in turn activates melanocortin neurons in the CNS. D-FEN is also known to increase the release of serotonin from the brain, a hormone also thought to be involved in eating disorders such as anorexia nervosa.

The researchers studied activity patterns in the arcuate nucleus region of the hypothalamus, which is an area of the brain in which serotonin is received directly by pro-opiomelanocortin (POMC) neurons. On activation, these neurons stimulate the release of peptide molecules that act on melanocortin receptors, which are crucial regulators of appetite, energy and hormones in the brain. The researchers found that the firing rate of POMC neurons was doubled by the presence of D-FEN and that the neurons depolarized in response to receiving D-FEN, serotonin or either of two serotonin receptor antagonists.

'Our study has linked the serotonin system, a classic brain pathway thought to be involved with eating disorders like anorexia nervosa, to the melanocortin system, a brain pathway involved in obesity', reported Elmquist, who added; 'our work gives a mechanistic explanation of how drugs like D-FEN may inhibit food intake'. These results could lead to the development of novel drugs for the prevention and treatment of obesity that have fewer side effects than D-FEN itself, which was withdrawn by the FDA after reports of cardiac complications.

1 Heisler, L.K. *et al.* (2002) Activation of central melanocortin pathways by fenfluramine. *Science* 10.1126/science.1072327

New tools for diagnosing muscular dystrophies?

A new molecular mechanism recently reported as being the possible cause of a subset of muscular dystrophies [2,3] could lead to the development of improved diagnostic and prognostic tools for patients with this condition.

Muscular dystrophy covers a range of conditions, most of which gradually destroy muscle. However, there is a subset that also cause brain abnormalities that result in severe mental retardation, for example, Fukuyama congenital muscular

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