Vaccination with prion peptide-displaying papillomavirus-like particles induces autoantibodies to normal prion protein that interfere with pathologic prion protein production in infected cells.

Abstract:

Prion diseases are fatal neurodegenerative disorders caused by proteinaceous infectious pathogens termed prions (PrP(Sc)). To date, there is no prophylaxis or therapy available for these transmissible encephalopathies. Passive immunization with monoclonal antibodies recognizing the normal host-encoded prion protein (PrP(C)) has been reported to abolish PrP(Sc) infectivity and to delay onset of disease. Because of established immunologic tolerance against the widely expressed PrP(C), active immunization appears to be difficult to achieve. To overcome this limitation, papillomavirus-like particles were generated that display a nine amino acid B-cell epitope, DWEDRYYRE, of the murine/rat prion protein in an immunogenic capsid surface loop, by insertion into the L1 major capsid protein of bovine papillomavirus type 1. The PrP peptide was selected on the basis of its previously suggested central role in prion pathogenesis. Immunization with PrP-virus-like particles induced high-titer antibodies to PrP in rabbit and in rat, without inducing overt adverse effects. As determined by peptide-specific ELISA, rabbit immune sera recognized the inserted murine/rat epitope and also cross-reacted with the homologous rabbit/human epitope differing in one amino acid residue. In contrast, rat
immune sera recognized the murine/rat peptide only. Sera of both species reacted with PrP(C) in its native conformation in mouse brain and on rat pheochromocytoma cells, as determined by immunoprecipitation and fluorescence-activated cell sorting analysis. Importantly, rabbit anti-PrP serum contained high-affinity antibody that inhibited de novo synthesis of PrP(Sc) in prion-infected cells. If also effective in vivo, PrP-virus-like particle vaccination opens a unique possibility for immunologic prevention of currently fatal and incurable prion-mediated diseases.