Humoral immune response to native eukaryotic prion protein correlates with anti-prion protection.

Prion diseases are characterized by the deposition of an abnormal form (termed PrP(Sc)) of the cellular prion protein (PrP(C)). Because antibodies to PrP(C) can antagonize deposition of PrP(Sc) in cultured cells and mice, they may be useful for anti-prion therapy. However, induction of protective anti-prion immune responses in WT animals may be hindered by host tolerance. Here, we studied the cellular and molecular basis of tolerance to PrP(C). Immunization of Prnp(o/o) mice with bacterially expressed PrP (PrP(REC)) resulted in vigorous humoral immune responses to PrP(REC) and native cell-surface PrP(C). Instead, WT mice yielded antibodies that failed to recognize native PrP(C) despite immunoreactivity with PrP(REC), even after immunization with PrP-PrP polyprotein and/or upon administration of anti-OX40 antibodies. Consequently, immunized WT mice experienced insignificantly delayed prion pathogenesis upon peripheral prion challenge. Anti-PrP immune responses in Prnp(o/o) mice were completely abrogated by transgenic expression of PrP(C) in B cells, T cells, neurons, or hepatocytes, but only moderately reduced by expression in myelinating cells, despite additional thymic Prnp transcription in each case. We conclude that tolerance to PrP(C) can coexist with immunoreactivity to PrP(REC) and does not depend on...
thymic PrP(C) expression. Its circumvention might represent an important step toward the development of effective anti-prion immunotherapy.