Multiple amino acid residues within the rabbit prion protein inhibit formation of its abnormal isoform.

Transmissible spongiform encephalopathies (TSEs) are neurological diseases that are associated with the conversion of the normal host-encoded prion protein (PrP-sen) to an abnormal protease-resistant form, PrP-res. Transmission of the TSE agent from one species to another is usually inefficient and accompanied by a prolonged incubation time. Species barriers to infection by the TSE agent are of particular importance given the apparent transmission of bovine spongiform encephalopathy to humans. Among the few animal species that appear to be resistant to infection by the TSE agent are rabbits. They survive challenge with the human kuru and Creutzfeldt-Jakob agents as well as with scrapie agent isolated from sheep or mice. Species barriers to the TSE agent are strongly influenced by the PrP amino acid sequence of both the donor and recipient animals. Here we show that rabbit PrP-sen does not form PrP-res in murine tissue culture cells persistently infected with the mouse-adapted scrapie agent. Unlike other TSE species barriers that have been studied, critical amino acid residues that inhibit PrP-res formation are located throughout the rabbit PrP sequence. Our results suggest that the resistance of rabbits to infection by the TSE agent is due to multiple rabbit PrP-specific amino acid residues that result in a PrP structure that is unable to refold to the abnormal isoform associated with disease.