Single treatment with RNAi against prion protein rescues early neuronal dysfunction and prolongs survival in mice with prion disease

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Abstract

Prion diseases are fatal neurodegenerative conditions for which there is no effective treatment. Prion propagation involves the conversion of cellular prion protein, PrP(C), to its conformational isomer, PrP(Sc), which accumulates in disease. Here, we show effective therapeutic knockdown of PrP(C) expression using RNAi in mice with established prion disease. A single administration of lentivirus expressing a shRNA targeting PrP into each hippocampus of mice with established prion disease significantly prolonged survival time. Treated animals lived 19% and 24% longer than mice given an "empty" lentivirus, or not treated, respectively. Lentivirally mediated RNAi of PrP also prevented the onset of behavioral deficits associated with early prion disease, reduced spongiform degeneration, and protected against neuronal loss. In contrast, mice receiving empty virus or no treatment developed early cognitive impairment and showed severe spongiosis and neuronal loss. The focal use of RNAi therapeutically in prion disease further supports strategies depleting PrP(C), which we previously established to be a valid target for prion-based treatments. This approach can now be used to define the temporal, quantitative, and regional requirements for PrP knockdown for effective treatment of prion disease and to explore mechanisms involved in predegenerative neuronal dysfunction and its rescue.


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