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New prion strain generation through splenic replication

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Prion aggregates typically spread from their entry site into the central nervous system. However, distinct prion conformers show varying capacity to penetrate the CNS, as certain fibrillar prions replicate persistently in the spleen without CNS access, leading to silent carriers. Subclinical carriers of variant Creutzfeldt-Jakob (vCJD) prions in the United Kingdom have been estimated at 1:2000, and vCJD prions have been transmitted by blood transfusion from prion-infected donors. Yet it remains unclear which types of circulating prion conformers will neuroinvade following a transfusion. To understand how prion conformation impacts brain entry of transfused prions, we challenged mice intravenously to five subfibrillar and fibrillar strains. We found that all subfibrillar prions infiltrated the brain and caused terminal disease, however the fibrillar prions showed reduced CNS entry in a strain-dependent manner. Whereas one fibrillar prion efficiently spread to the CNS with no apparent strain change, a second fibrillar prion replicated in the spleen and emerged in the brain as a novel strain. The new strain showed an altered plaque morphology, targets in brain, and biochemical properties as compared to the original strain, and these properties were maintained upon further passage. Direct intracerebral passage of prion-infected spleen also generated the new strain, suggesting splenic replication as a potential source. Taken together, these results indicate that exposure to prion-contaminated blood or blood products may produce novel prion conformers and disease phenotypes, potentially arising from prion replication by non-neural cell types or from selection of a neuroinvasive conformer.

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