IS AD A PRION DISEASE? YES

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In recent years, there has been an increasing body of evidence that certain neurodegenerative diseases and their major proteins have prion-like qualities and in many cases are even transmissible. These diseases include Alzheimer's disease, Parkinson's disease, Huntington's disease, Multiple System Atrophy, ALS, Progressive supranuclear palsy and other tauopathies, as well as others. In these disorders there is evidence that proteins misfolds and that these misfolded proteins spread from cell to cell in the brain. Propagation of protein misfolding in these diseases might occur through mechanisms similar to those that underlie prion pathogenesis. The evidence that these proteins and accompanying diseases are prion-like has ranged from in vitro evidence showing cell to cell spread of self-propagating proteins, to *in vivo* animal models of disease transmission by direct inoculation. This is particularly true for Alzheimer's disease, in which the two primary proteins involved, Aß amyloid and tau, have been shown to be transmissible. This perhaps is not surprising as the Braaks showed more than 20 years ago how AD spreads in the brain during the course of disease from the entorhinal cortex to the hippocampus, to the parietal lobes and then to other cortical regions. Baker, Riley and colleagues also showed more than 20 years ago how cerebral beta-amyloidosis could be transmitted experimentally to marmosets. The exogenous induction of cerebral amyloidosis also has been shown in other non-human primates and mice. More recently, in 2006, AD brain homogenates were inoculated into marmosets causing development of Aß amyloid plaques after incubation periods of more than 3.5 years. The same year, A few groups have independently now shown the transmission of AD brain in transgenic AD mice. Perhaps the strongest support for transmissibility, and prion-like characteristics, of AD, has come from Jan Stohr and colleagues in the Prusiner laboratory showing inoculation of brain-derived purified Aß aggregates or synthetic Aß aggregates were each capable of inducing Aß deposition in vivo.

Not only has Aß shown to be transmissible, but tau has as well. Some of the initial and most elegant work on the prion-like properties of tau has come from the in work of Bess Frost, Marc Diamond and colleagues showing cell to cell propagation of tau. Lee, Trojanowski and colleagues have shown that synthetic tau fibrils are sufficient to transmit tau inclusions in a tauopathy mouse model transmission and spread of tau. Interestingly, this resulted in propagation of neurofibrillary tangle like inclusions to connected brain region.

In AD, as two proteins are predominantly involved and both have been shown to be transmissible, AD perhaps should be considered a double prion disease. As with prion diseases in which different conformations of prions cause different forms of prion diseases, different conformations of tau and/or Aß might also explain the varied presentations or phenotypes of AD, both sporadic and genetic forms.

One issue with calling AD a prion disease deals with whether or not it is infective or transmissible from person to person, as occurs with some, but not all prion diseases. In fact, less than 1% of prion diseases are known to be infectious or acquired. Although the proteins of AD, tau and Aß are transmissible from cell to cell, it is not clear that these proteins are truly infectious in the way prion diseases are. Matthias Jucker and colleagues have shown that wires dipped in Aß containing brain extracts can transmit Aß amyloidosis in APP23 mice, much like the way prion diseases can be transmitted experimentally or iatrogenically. It appears that AD proteins are much easier to decontaminate from these wires than typical prions. It is possible that AD is infectious, but infectious has not occurred or is exceedingly rare because Aß and/or tau are more easily "decontaminated" than prions, the Aß and tau prions are less efficient, and/or the incubation period is much longer than for prions. Perhaps whether or not AD is infectious is less important than the concept of cell to cell propagation of misfolded proteins as a mechanism for disease spread for which interventions might be developed.