The Seeding and Transmissibility of Tau, Aβ and Synuclein Aggregates

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One of the most striking and surprising aspects of prion diseases was the transmissibility of disease through a proteinaceous infectious particle (see main text). For many years, this property was thought to be unique to the prion protein gene product, but recent studies suggest that a more general principle may be involved in the mechanisms of prion transmissibility. Indeed, the evidence is mounting that some non-prion protein aggregates can be transmitted from one cell to a neighboring cell (Cushman et al., Frost & Diamond, 2010; Goedert et al., 2010; Lee et al., 2010), and these events may play a role in pathogenesis for diseases that include Alzheimer's (AD) and Parkinson's (PD) among others. Although none of these diseases exhibit infectivity in the same sense as prions, these mechanisms could contribute to the temporospatial spreading of pathology often observed in these diseases (Goedert et al., 2010).

Tau, Aβ42 peptide and synuclein are all polypeptides with multiple, dynamic conformations, but they can become locked into specific conformations that act as self-templates for higher-order aggregates (Lee et al., 2010). This is a property shared with the prion protein and is thought to be an essential element of pathogenicity in prion diseases as well as in AD and PD. Specific conformations of tau, Aβ or synuclein appear to be associated with neurotoxicity. For example, filamentous forms of tau activate GSK3 kinase, a property that is not shared with soluble monomeric tau (Lapointe et al., 2009). Extracellular aggregates of tau are taken up by cells in culture and can seed formation of similar aggregates (Frost et al., 2010; Goedert et al., 2010).

Aβ42 peptides exist in unaggregated, oligomeric or filamentous immunologically distinct forms *in vivo* (Sakono & Zako, 2010). Several lines of evidence suggest that oligomeric forms of

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Aβ42 are significantly more toxic. For example, oligomeric Aβ42, but not unaggregated or fibrillar forms, inhibit fast axonal transport and produce synaptic failure (Moreno et al., 2009; Pigino et al., 2009). Remarkably, both intracerebral and peripheral injection of Aβ42 amyloid can lead to amyloidosis and tau pathology in vulnerable cells expressing human APP and tau (Frost & Diamond, 2010; Goedert et al., 2010).

Finally, synuclein fibril formation can be nucleated by existing oligomers or fibrils (Frost et al., 2010) much like tau or Aβ42. Studies with neurons in culture expressing mutant synuclein associated with familial forms of PD indicate that synuclein aggregates can be released from cells and taken up by others, leading to Lewy-type pathology (Cushman et al., 2010; Frost et al., 2010). Moreover, patients who have received mesencephalic dopaminergic neuron grafts can exhibit host-to-graft spreading of Lewy pathology (Goedert et al., 2010).

The evidence is compelling that such transmissibility can occur with tau, Aβ and synuclein aggregates. Rather less certain is the extent to which this pathway contributes to the disease process in human patients. Studies that show elevated tau and synuclein conformers in cerebrospinal fluid of patients appear to correlate with neuropathology (Blennow et al., 2010; Eller & Williams, 2009) and these elevated levels are increasingly used as biomarkers for diagnostic purposes. Such findings indicate that disease-associated forms of tau and synuclein can be released into the extracellular environment, but more work is needed to determine whether this release is a consequence of neurodegeneration or whether it contributes to the spread of pathology.

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