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Editorial: Pathogenic templating proteins in Neurodegenerative Disease

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Most neurodegenerative diseases are characterized by proteinaceous aggregates with a defined protein structure called amyloid fibrils which are assemblies of protofilaments with cross- β structure. Abundant evidence demonstrates that these aggregates form by the *de novo* misfolding of normal proteins into beta sheet conformations that corrupt and recruit additional protein monomer to form oligomers and amyloid fibrils. This concept, called pathogenic templating, emerged from studies of prion disease. Pathogenic templating has been demonstrated in almost all progressive neurodegenerative diseases (Jucker and Walker, 2013) including amyloid β (Ahmed et al., 2014; Duran-Aniotz et al., 2014; Eisele et al., 2010; Kane et al., 2000; Langer et al., 2011; Meyer-Luehmann et al., 2006; Stohr et al., 2014; Stohr et al., 2012; Walker et al., 2002) and tau (Ahmed et al., 2014; Clavaguera et al., 2013; Iba et al., 2013) in Alzheimer's disease; α -synuclein in Parkinson's disease (Luk et al., 2012; Luk et al., 2009; Nonaka et al., 2010; Volpicelli-Daley et al., 2011); huntingtin in Huntington's disease (Jeon et al., 2016; Pecho-Vrieseling et al., 2014; Ren et al., 2009; Tan et al., 2015), TDP-43 in frontotemporal dementia (Furukawa et al., 2011; Shimonaka et al., 2016) and superoxide dismutase-1 in amyotrophic lateral sclerosis (Ayers et al., 2016; Grad et al., 2011; Munch et al., 2011). The abnormal protein conformers likely spread across interconnected neuronal networks where they further corrupt endogenous proteins.

There are several lines of evidence supporting the self-propagation activity of aggregates implicated in neurodegenerative disease. First, Braak staging studies of Parkinson's disease and Alzheimer's disease map pathology in postmortem brains from early stages of disease to those with advanced stages of the disease (Braak and Braak, 1991; Braak and Braak, 1995; Braak et al., 2003). These studies suggest that formation of Lewy pathology, neurofibrillary tangles and amyloid plaques in general follows a predictable temporal and spatial pattern. In addition, fetal nigral grafts placed in the striatum of PD patients eventually develop Lewy bodies, suggesting the new grafted neurons generate α -synuclein aggregates after taking up misfolded α -synuclein released from diseased neurons in the host brain (Kordower et al., 2008; Kordower et al., 2011; Kurowska et al., 2011; Li et al., 2008; Li et al., 2010). In

animal models of neurodegenerative disease, injection of extracts rich in A β plaques, neurofibrillary tangles or Lewy pathology into brains of young animals can induce and accelerate development of pathology (Ahmed et al., 2014; Clavaguera et al., 2013; Kane et al., 2000; Masuda-Suzukake et al., 2013; Meyer-Luehmann et al., 2006; Mougenot et al., 2012; Prusiner et al., 2015; Recasens et al., 2014; Walker et al., 2002; Watts et al., 2013).

Immunodepletion of these aggregates with antibodies specific to α -synuclein, tau or A β prevents inclusion formation (Clavaguera et al., 2013; Masliah et al., 2005; Meyer-Luehmann et al., 2006; Spencer et al., 2017; Tran et al., 2014), demonstrating that the protein aggregates themselves, and not a factor found in the extract, induces protein inclusion formation. Exposure of neurons to fibrils generated from recombinant α -synuclein (Luk et al., 2012; Masuda-Suzukake et al., 2013; Paumier et al., 2015; Volpicelli-Daley et al., 2011) or tau (Iba et al., 2013; Peeraer et al., 2015) results in their uptake and induction of neuronal pathology. Importantly, the inclusions induced from the fibrillar seeds resemble those found in diseased brains both morphologically and biochemically such as insolubility in anionic detergents and resistance to digestion with proteinase K. Furthermore, injection of the pathologic aggregates can induce pathology in distal sites not directly connected to the area in which the aggregates were injected. For example, olfactory bulb injections of α -synuclein fibrils over time results in pathology in over 40 brain regions, sometimes two or more synapses away from the injection site, including brain stem regions such as the substantia nigra, locus coeruleus, and raphe nucleus (See Rey et al, article 6 (Rey et al., 2013; Rey et al., 2016; Rey et al., 2017)). Intramuscular injections of α -synuclein fibrils produce pathology in the central nervous system (Sacino et al., 2014). Intraperitoneal injections of extracts containing A β can induce formation of plaques in the brain (Eisele et al., 2010). Thus, these data support that the seeds can travel transsynaptically between brain regions.

Findings demonstrating pathogenic templating of proteins have led to discovery of novel therapeutic strategies to prevent the self-propagation of these neurodegenerative diseases (Brundin et al., 2017). First, passive or active immunotherapies can prevent the spread of pathogenic seeds across the nervous system and reduce pathology and associated behavioral phenotypes (George and Brundin, 2015; Spencer et al., 2017; Valera et al., 2016). The development of antibodies that selectively target misfolded conformers may be beneficial to reduce potential side effects caused by targeting the endogenous, normal conformation of the protein (See Cremades et al, article 1). Compounds to reduce aggregation or disrupt aggregates are in preclinical trials (Brundin et al., 2017; Krishnan et al., 2017; Wrasidlo et al., 2016). Antisense oligonucleotides have emerged as promising strategies to treat neurodegenerative diseases (Ottesen, 2017). Reducing expression of the monomeric protein may prevent its conversion to the misfolded, aggregate-prone form. For example, ASO-mediated reduction of tau prevents tau aggregation and neurodegeneration in a mouse tauopathy model (DeVos et al., 2017). Identification of receptors that facilitate the uptake of the aggregates may also provide a therapeutic target because inhibitors of internalization of the seeds would prevent them from templating pathology inside the neuron (Mao et al., 2016). Finally, understanding how genes implicated in these neurodegenerative diseases facilitate pathogenic templating could lead to novel therapeutics. For example, mutations in glucocerebrosidase and leucine rich repeat kinase 2 increase the risk of PD, and both

proteins influence α -synuclein aggregation and both can be targeted pharmacologically (Fishbein et al., 2014; Lin et al., 2009; Mazzulli et al., 2011; Sardi et al., 2013; Volpicelli-Daley et al., 2016; Xiong et al., 2017; Xu et al., 2011). In Alzheimer's disease, the APOE4 allele increases the risk of developing AD and influences formation of A β plaques and tau aggregates. Targeting APOE4 may prevent the progression of AD (Mahley, 2016).

There remain several outstanding questions that require a combination of basic laboratory investigation and translational research to help us understand the contribution of pathogenic templating to neurodegenerative disease pathogenesis:

- *What are the triggers that cause the protein to convert from a normal conformation to an abnormal conformation prone to aggregate?* Potential culprits include inflammation and mitochondrial dysfunction, pesticides and environmental toxins (see Sanders et al, article 7), perturbations in the gut microbiome (Hill-Burns et al., 2017; Sampson et al., 2016) and, of course, increased age of the individual (Chu and Kordower, 2007). Also, slightly increased levels of the protein may enhance its aggregation (Devine et al., 2011; Farrer et al., 2004; Miller et al., 2004; Singleton et al., 2003; Soldner et al., 2016).
- *Where in the body does the pathogenic templating initiate; in neurons in central brain regions or parts of the nervous system that have direct contact with the outside environment, such as the olfactory bulb or gastrointestinal tract?* (see Rey et al article 6 (Rey et al., 2016b)).
- *What is the conformer of the aggregate responsible for seeding and neuron toxicity? Are the conformers responsible for seeding amyloid fibrils distinct from those that and cause neurodegeneration?* (see Cremades et al article 1 (Cremades and Dobson, 2017)).
- While fibrils spread from cell to cell, are they the toxic species? Or, are soluble oligomers in the pathway to fibril formation more toxic?
- Do the aggregates induce neurodegeneration by causing a toxic gain of function, or reducing the function of the normal protein?
- *Are there different strains of protein aggregates that produce different disease phenotypes?* (see Stoehr et al. article 2 (Condello and Stoehr, 2017), Melki article 3 (Melki, 2017), Peng et al. article 4 (Peng et al., 2017)). If so, different therapeutic strategies such as antibodies that specifically target one conformation of aggregate may need to be developed for each disease subtype (Cremades et al. article 1 (Cremades and Dobson, 2017)).
- *Can one protein aggregate induce aggregation of another protein?* For example, Lewy pathology, and neurofibrillary tangles can sometimes be found in the same brain regions and within the same neuron. Formation of α -synuclein inclusions may sequester a factor that maintains tau in a normal conformation. Removal of this factor may induce tau aggregation (see Melki article 3 (Melki, 2017)).

- *How do these aggregates spread within the neuron? How are they released? How are they taken up by neighboring neurons (see Bieri article 5 (Bieri et al, 2017))?*
- *Is the corruption of one protein alone sufficient to induce neurodegeneration, or are there a combination of factors involved, such as both inclusion formation and activation of inflammatory pathways (Valera and Masliah, 2016)?*
- Amyloid proteins play a normal physiological role. For example, *Escherichia coli* produce amyloid fibrils called curli which facilitate interaction with host proteins. Biogenesis of melanosomes, lysosome related organelles, relies on amyloid fibrils made of a protein, Pmel17 (Chiti and Dobson, 2006). *Do the amyloid proteins implicated in neurodegenerative disease play normal roles in cell physiology?* The recent finding that the LAG3 receptor selectively binds α -synuclein fibrils suggests that the fibrils may play some role in the neuron (Mao et al., 2016). Another study shows that α -synuclein is important for initiating inflammatory responses to infection (Stolzenberg et al., 2017), and might even function as a protein that restricts viral infections (Beatman et al, 2015; Massey and Beckham, 2016). Perhaps what protects us early on can lead to neurodegeneration many years later.
- *Are there naturally occurring mutations in these proteins that protect from amyloid formation?* For example the Glycine 127 to Valine mutations in PrPc confers resistance to Kuru (Asante et al., 2015). Similar protective mutations may exist in α -synuclein, amyloid precursor protein or tau.

Overall, the discovery of pathogenic templating in neurodegenerative disease has opened an important new field for understanding mechanisms of disease pathogenesis and design of new therapeutic strategies to prevent the formation and spread of these destructive aggregates and halt disease progression.

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