In Vivo Spreading of Tau Pathology

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Recent findings have suggested that tau pathology may spread in the brain by a prion-like mechanism. In this issue of *Neuron*, de Calignon et al. (2012) recreated an early stage of neurofibrillary tangle pathology to show that tau aggregates initially generated in a circumscribed area spread throughout the brain and lead to neurodegeneration.

Neurofibrillary tangles (NFTs) composed of a misfolded and aggregated form of tau are a hallmark event in the pathogenesis of Alzheimer's disease (AD) and other neurodegenerative disorders, often called tauopathies, which include fronto-temporal dementia, Pick's disease, and chronic traumatic encephalopathy, among others. In spite of compelling evidence indicating that NFTs play a major role in neurodegeneration, little is known about the mechanism and factors implicated in the initiation and spreading of this pathology in the brain.

Misfolding and aggregation is not a unique feature of tau; indeed, misfolded protein aggregates are implicated in more than 20 human diseases, collectively called protein misfolding disorders (PMDs). The PMD group comprises highly prevalent and insidious illnesses including AD, Parkinson's disease, and type 2 diabetes, as well as rarer disorders, such as Huntington's disease, systemic amyloidosis, amyotrophic lateral sclerosis, and transmissible spongiform encephalopathies (TSEs) (Chiti and Dobson, 2006; Moreno-Gonzalez and Soto, 2011). Although the proteins implicated in each of these pathologies and the clinical manifestations of the diseases differ, the molecular mechanism of protein misfolding and the structural intermediates and endpoint of the protein aggregation are remarkably similar. Among PMDs, TSEs, also known as prion diseases, are the ones in which the causative role for the accumulation of misfolded protein aggregates are best established. This is because TSEs can be acquired by infection, and compelling evidence indicates that the misfolded prion protein is the main (if not the sole) component of the infectious agent (Soto, 2011). TSEs are transmitted by the autocatalytic conversion of the natively folded prion protein seeded by the misfolded version of the protein. In this manner, misfolded prion aggregates spread throughout the body and can occasionally, through defined routes, transmit between individuals to propagate the disease. Until recently, the spreading and transmission of disease by propagation of protein misfolding was thought to be an oddity of the rogue prion protein. However, a series of recent and exciting studies has shown experimental evidence for prion-like mechanisms of pathological spreading of misfolded proteins associated to various diseases (Aguzzi and Rajendran, 2009; Brundin et al., 2010; Moreno-Gonzalez and Soto, 2011).

Various in vitro and in vivo studies have reported that tau aggregates can spread in the brain by a prion-like mechanism. Experiments in cultured cells have shown that extracellular tau aggregates can be endocytosed by cells and can act as seeds to induce the misfolding and aggregation of intracellular tau (Frost et al., 2009; Guo and Lee, 2011; Nonaka et al., 2010). These intracellular tau aggregates can further spread among cells to extend the pathology to the entire culture. Intracerebral injection of brain extract containing tau aggregates into transgenic mice expressing human wild-type tau induced the conversion of the native protein into NFT-like aggregates in recipient mice (Clavaguera et al., 2009). Interestingly, the pathology spread over time beyond the site of injection to synaptically connected neighboring brain regions (Clavaguera et al., 2009). These findings may provide a mechanistic explanation for the long-known, but puzzling, observation that formation and accumulation of NFTs in AD progresses with time in a stepwise characteristic pattern. NFTs initiate in a circumscribed area of the entorhinal cortex, and pathology progresses in a topographically predictable manner across limbic and association cortices through anatomical connections (Braak and Braak, 1991).

The elegant experiments reported in this issue of *Neuron* by de Calignon et al. (2012) provide further support for the concept that NFTs spread in the brain by a prion-like mechanism, probably accounting for the stereotypical progression of NFT pathology in AD. A bigenic mice model (termed rTgTauEC) in which overexpression of human mutant (P301L) tau is restricted to the layer II of the entorhinal cortex (EC) was used for these studies. In this way, the authors recreated an early stage of AD NFT pathology to investigate how tau aggregates generated in a circumscribed area, spread throughout the brain, and led to neurodegeneration. The rTgTauEC mouse model was generated by using a previously described tetO-human P301L tau mouse that only expresses the human tau gene in the presence of a tet-transactivator crossed with a mouse that expresses the transactivator protein under the control of the neuroserpin promoter. A detailed analysis of the human mutant tau gene expression by various techniques showed that the mRNA and the protein were detectable mainly in the superficial layers of the medial EC and the closely related pre- and parasubicular cortices. Using this model, the authors examined the appearance and progression of tau pathology in

diverse areas of the brain in animals of different ages. The results show that tau pathology starts in neurons of the EC expressing the human transgene and over time progresses to cells without detectable human tau expression, first in the vicinity of the EC and later in more distant regions located downstream in the synaptic circuit, such as the dentate gyrus, hippocampus, and cingulate cortex. Human tau protein appears to spread to these brain regions and to interact with and induce aggregation of endogenous mouse tau. The progressive accumulation of tau aggregates leads to synaptic degeneration and later to axonal damage and neuronal death.

The exquisite regional specificity of the human transgene expression combined with the use of sophisticated techniques to analyze the brain of these animals enabled the authors to obtain a number of important conclusions, namely: (1) tau aggregates can transfer to neighboring cells and to synaptically connected neurons in distant parts of the brain, all of which do not express detectable levels of the human protein; (2) misfolded human mutant tau recruits endogenous mouse tau into the aggregates, leading to its progressive intraneuronal accumulation; (3) spreading of tau pathology induces a slow synaptic destruction, followed by axonal and later somatic degeneration of neurons. These are important findings in order to understand the progression of tau pathology and associated damage in AD, and they fit well with recent observations indicating that tau misfolding and aggregation can spread from cell to cell in a prion-like manner (Clavaguera et al., 2009; Frost et al., 2009; Guo and Lee, 2011; Nonaka et al., 2010). However, a potential weakness of the current study is that, despite all the diverse techniques used to evaluate human tau expression, the authors cannot completely rule out a low expression (below the level of detection of the methods employed) of the transgene in other brain areas. Indeed, some leakiness of expression has been reported previously for similar mouse models (Santacruz et al., 2005). In this scenario, low widespread expression of human P301L tau, and not spreading of aggregates from one site to another, may have seeded aggregation of endogenous mouse tau and triggered neurodegeneration. Although the authors provide convincing evidence that expression beyond the targeted areas must be very low (or nonexistent), it is also noticeable that because of the high efficiency of the seeding process, these minute quantities may be enough to induce tau aggregation.

A series of recent and exciting studies has provided strong support for the concept that the accumulation of misfolded protein aggregates, which is intimately associated to the pathogenesis of various neurodegenerative diseases, is mediated by the intercellular spreading of oligomeric seeds (Aguzzi and Rajendran, 2009; Brundin et al., 2010). In a manner similar to the infamous prions, misfolded oligomers composed by diverse proteins can act as a template to induce the conversion of natively folded proteins, propagating the abnormalities to other cells, tissues, and organs. In the case of tau pathology, the current study by de Calignon et al., in addition to various recent reports from other groups (Clavaguera et al., 2009; Frost et al., 2009; Guo and Lee, 2011; Nonaka et al., 2010), indicates that misfolding and aggregation of tau may start in a restricted area of the brain and from there spread toward other regions through synaptic connections, leading to a progressive amplification of the damage and expansion throughout the brain. Many open questions regarding this prion-like phenomenon of spreading of tau misfolding still need to be addressed, including the following four points.

(1) What are the factors and mechanisms responsible for the formation of the first misfolded tau seeds? In the present study, pathology was initiated by artificial expression of a human mutant version of the tau gene in a defined brain area. In the study by Clavaguera and colleagues (2009), the seeds were introduced by direct intracerebral injection of brain homogenates containing tau aggregates. It is possible to envision at least three different ways in which the initial seeds may arise. First, seeds may be formed spontaneously in a particular area of the brain, perhaps as a consequence of somatic mutations, transcriptional/translational errors, defects of the proteostasis machinery, or tissue injury (e.g., brain trauma or subclinical stroke), all of which are probably more frequent during aging. Second, the initial seeds may be acquired exogenously through an ''infection-like'' process of exposure to preformed aggregates. In prion diseases, transmission between individuals can occur through medical practices (e.g., blood transfusion, organ transplants, and use of materials or surgical tools contaminated with prions), consumption of food from animals carrying misfolded prions, or vertical transmission (Will, 2003). Third, misfolded aggregates composed of one protein may interact and promote the aggregation of another protein by a phenomenon known as cross-seeding. Evidence for this process has been found for several PMDs, using animal models, in vitro systems, and human epidemiological analysis (see Morales et al., 2009 and references therein). It is also possible that non-disease-associated aggregates (so-called functional amyloids) may also induce misfolding of disease-related proteins through cross-seeding (Johan et al., 1998).

(2) What are the mechanisms responsible for the transference of tau seeds between cells? Studies with cellular models of tau and α-synuclein suggest that intracellular aggregates gain access to the extracellular space either by secretion or by damage of the host cell (Guo and Lee, 2011; Nonaka et al., 2010). Thereafter, extracellular aggregates can get internalized to neighboring cells, most likely through endocytosis, allowing them to bind the natively folded protein and seed the misfolding and aggregation process (Frost et al., 2009; Guo and Lee, 2011; Nonaka et al., 2010). There have also been reports indicating that cell-to-cell spreading may occur through direct cellular contact, involving nanotubes, or mediated by exosomes or microvesicles (Aguzzi and Rajendran, 2009).

(3) What are the structural features of seed-competent misfolded proteins? Misfolded proteins consist of a heterogeneous mixture of aggregates of variable size. Elucidation of which of the different species is responsible for propagating the pathology is complicated by the lack of sufficient knowledge regarding the detailed structure of these aggregates and the dynamic nature of the aggregation process. Considering purely

physicochemical characteristics, it seems likely that freely circulating small oligomers may be better seeds; however, larger polymers may be more stable against biological clearance.

(4) What are the molecular bases for the selective cellular accumulation of NFTs? Even though spreading of tau pathology may provide a feasible explanation for the mechanism by which deposition of tau aggregates progresses in the brain of AD patients, this phenomenon does not explain why only some of the interconnected neurons develop NFTs. The reason behind the selective accumulation of different types of misfolded aggregates in distinct brain regions is a major unknown in the field. Possible explanations for this intriguing phenomenon could be the involvement of cellular receptors, the differential functioning of clearance mechanisms, or the distinct level of expression of the proteins involved in misfolding.

The finding that tau pathology spreads in the brain by a prion-like mechanism not only helps us understand the process involved in disease pathogenesis and provides a feasible explanation for the stereotypical progression of these lesions in AD brain but may also lead to the identification of new targets for therapeutic intervention. Indeed, preventing the initial formation of seeds or the subsequent spreading of tau aggregates may represent interesting strategies for a much-needed treatment for AD and related tauopathies.

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Bers-ERK Schwann Cells Coordinate Nerve Regeneration

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In this issue of *Neuron*, Napoli et al. (2012) demonstrate that elevated ERK/MAPK signaling in Schwann cells is a crucial trigger for Schwann cell dedifferentiation in vivo. Moreover, the authors show that dedifferentiated Schwann cells have the potential to coordinate much of the peripheral nerve response to injury.

A remarkable feature of the peripheral nerve is the ability to regenerate after injury. Regeneration is associated with an extraordinary series of changes in Schwann cells (reviewed in Chen et al., 2007). After injury, Schwann cells dedifferentiate into a progenitor-like state, proliferate, and repopulate the damaged nerve. In the nerve segment distal to the site of injury, columns of dedifferentiated Schwann cells form the Bands of Bungner and provide an important substrate for regenerating axons. Once axons have regenerated, Schwann cells then redifferentiate and remyelinate. Numerous axonal-, Schwann cell-, and immune-derived mediators are thought to be required for the regenerative response. Given the complex morphological changes and the number of mediators potentially involved, it would seem unlikely that the Schwann cell's multifaceted response to injury could be regulated by a single pathway.

Indeed, within hours of nerve injury, increased activity in multiple pathways including ERK/MAPK, JNK/c-Jun, Notch, and JAK-STAT can be detected in Schwann cells (Sheu et al., 2000; Woodhoo et al., 2009). In vivo studies have